SCIENTIFIC AMERICAN

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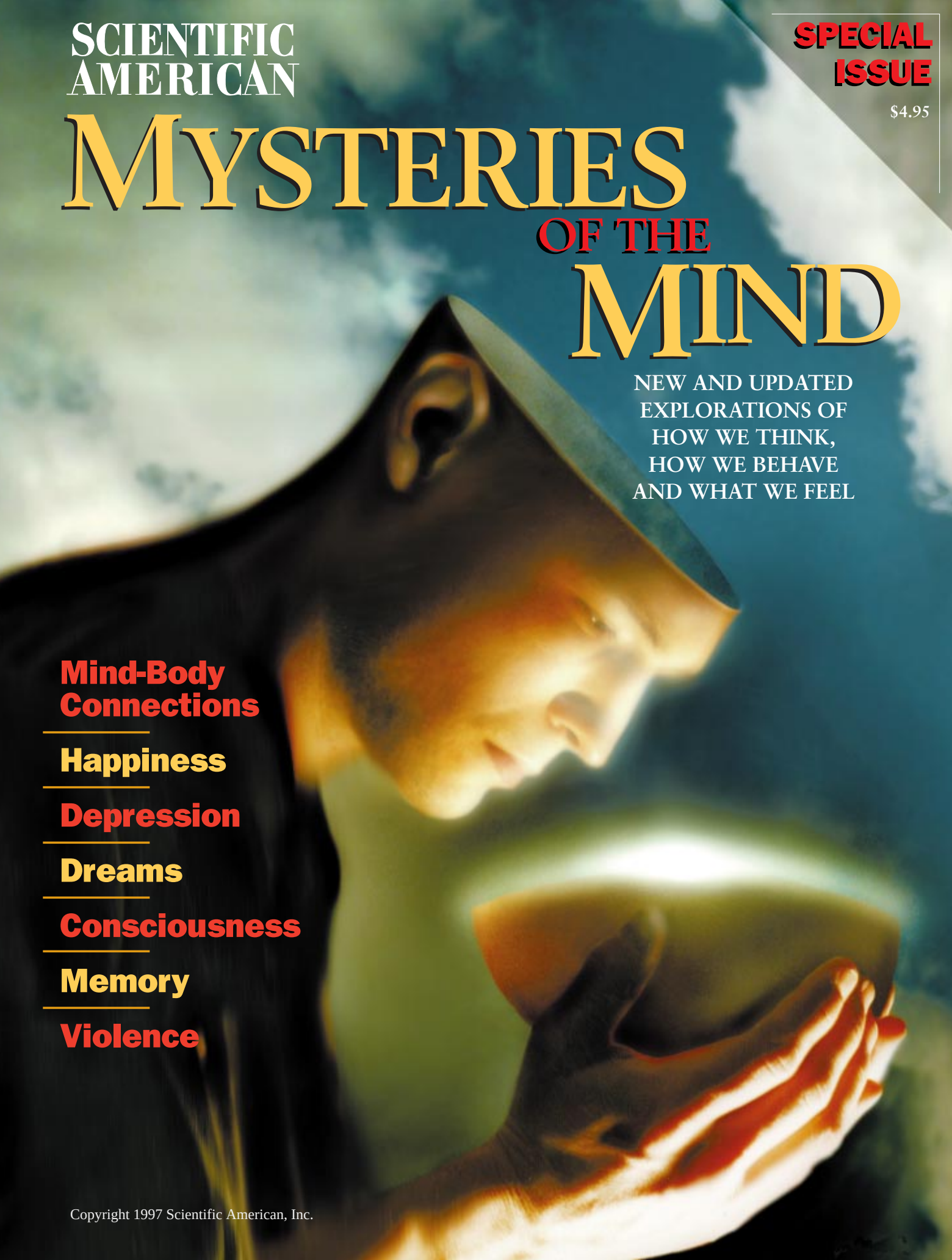
MYSTERIES OF THE MIND

NEW AND UPDATED EXPLORATIONS OF HOW WE THINK, HOW WE BEHAVE AND WHAT WE FEEL



- Mind-Body Connections
- Happiness
- Depression
- Dreams
- Consciousness
- Memory
- Violence

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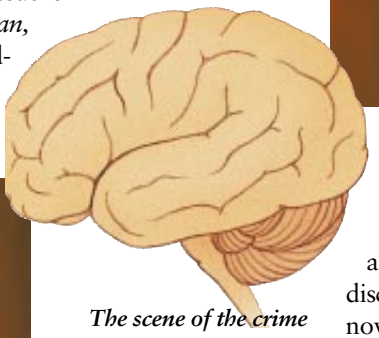
FROM THE EDITORS

The Persistent Mystery of Our Selves

Master detective Hercule Poirot, the hero of many an Agatha Christie novel, boasted repeatedly about the power of "the little gray cells" in his head to solve the toughest mysteries. For philosophers, writers and other thinkers, however, those little gray cells have been the greatest mystery of all. How do a couple of pounds of spongy, electrically active tissue give rise to a psychological essence? How do *we* emerge from the neural thicket?

Empirical scientists may be relative newcomers to this investigation (unlike the philosophers, they've been on the case for only a few hundred years), but they have taken long strides forward in that short time. In this special issue of *Scientific American*, some of the leading researchers in neuroscience and in psychology discuss how much is now known about the nature of consciousness, memory, emotions, creativity, dreams and other mental phenomena. Their answers suggest that some of these mysteries may be largely solved within our lifetimes—even if new ones are posed in the process.



The scene of the crime

But treat these articles as you would any good detective story: don't turn right to the end for the answers. Half the fun is in tracing the deductions.

JOHN RENNIE, *Editor in Chief*
editors@sciam.com

To be conscious that we are perceiving or thinking is to be conscious of our own existence.
—*Aristotle*

Memory is the cabinet of imagination, the treasury of reason, the registry of conscience, and the council chamber of thought.
—*St. Basil*

The whole machinery of our intelligence, our general ideas and laws, fixed and external objects, principles, persons, and gods, are so many symbolic, algebraic expressions.
—*George Santayana*

I have a prodigious quantity of mind; it takes me as much as a week sometimes to make it up.
—*Mark Twain*

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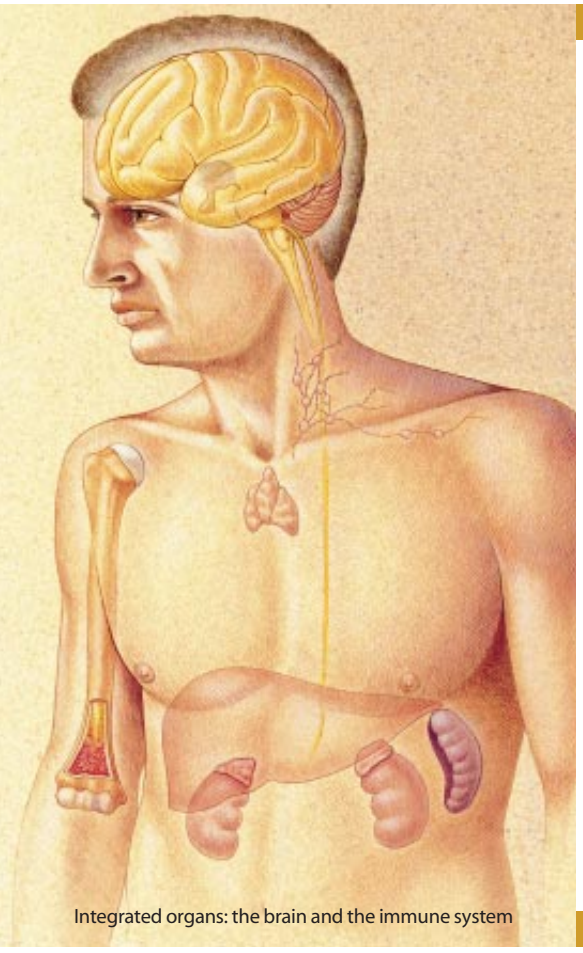
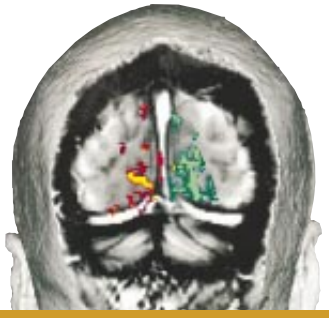
Mysteries of the Mind

8
The Mind-Body Interaction in Disease
Esther M. Sternberg and Philip W. Gold


Integrated organs: the brain and the immune system

Stress makes the body more vulnerable to some physical illnesses; immune responses can contribute to depression and fatigue. Even though the brain and the immune system differ in their functions and organization, they are interlinked at a subtle biochemical level. This fact suggests that drugs traditionally used to treat neurological problems might help against inflammatory maladies, and vice versa.

Scrutinizing the self


Patterns of excitement

18
The Problem of Consciousness
Francis Crick and Christof Koch

Neuroscientists are on the trail of how the physical brain gives rise to the psychological experience of mind. The key may be synchronous firing among sets of related neurons, generating coherence and meaning out of brain activity.

30
The Puzzle of Conscious Experience
David J. Chalmers

Might consciousness be an irreducible feature in nature, as basic as mass or electrical charge? Making that radical assumption, this philosopher claims, might be the only way for science to make sense of the subjective experience of self.

68
Emotion, Memory and the Brain
Joseph E. LeDoux

Emotional memories—such as the strongly felt associations behind phobias—form in a way that bypasses the brain's higher centers. This route ensures faster responses when danger looms.

76
The Neurobiology of Fear
Ned H. Kalin

Clues to excessive human anxiety can be found by studying fear in monkeys and other species. Their example may lead to the development of better therapies for frightened people.

An experience not soon forgotten

Alarm in the rhesus monkey

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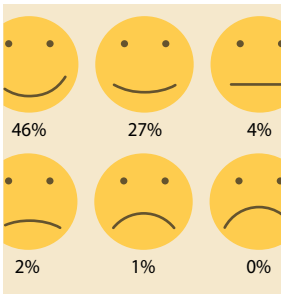
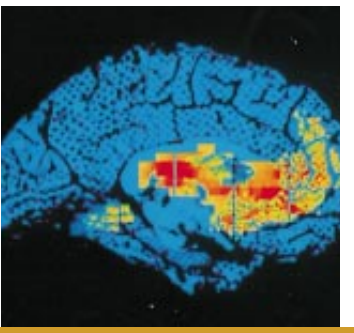


How do you feel today?

The moods of genius



Map of female sadness

Jacob's dream

40

The Pursuit of Happiness

David G. Myers and Ed Diener

Psychology has historically dwelled on the gloomier side of the human condition, but now joy is starting to get its share of attention. Surprisingly, people are more cheerful than one might suppose.

44

Manic-Depressive Illness and Creativity

Kay Redfield Jamison

Bouts of depression and manic energy are unusually common among gifted artists, musicians and writers. The painful roller coaster of their emotions may deepen their creative appreciation of the ambiguities of everyday life.

53

Depression's Double Standard

Kristin Leutwyler, staff writer

Around the world, the rates of depression are twice as high among women as among men. The reason is unclear, but biological differences between the sexes may contribute to this psychological gender gap.

58

The Meaning of Dreams

Jonathan Winson

Strangely meaningful images and bizarre flights of fancy may all be part of the dreaming brain's efforts to review memories, evaluate recent experiences and plot new strategies for surviving challenges in the waking world.

84

Phantom Limbs

Ronald Melzack

People who have lost an arm or leg sometimes still "feel" the missing part. Neurobiologists are beginning to understand more fully what creates this disturbing illusion.

92

Autism

Uta Frith

Autistic individuals seem lost in their own inner world. Their isolation stems from biological abnormalities that may in part interfere with the ability to imagine other people's mental states.

102

Seeking the Criminal Element

W. Wayt Gibbs, staff writer

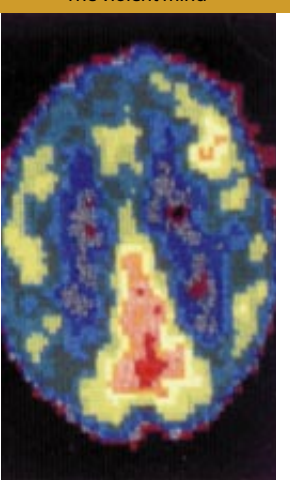
Identifying people with violent tendencies might be a great way to prevent crime. Or it could cause still greater injustice.

Cover image by Matt Mahurin.

Ghosts that feel real

Anguish of the autistic child

The violent mind



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The Mind-Body Interaction in Disease

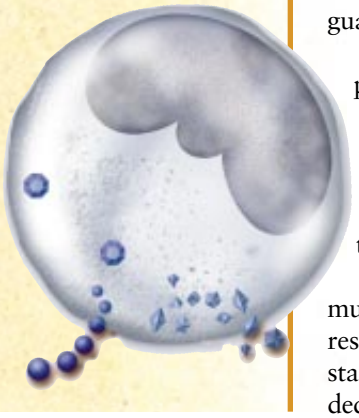
The brain and immune system continuously signal each other, often along the same pathways, which may explain how state of mind influences health

by Esther M. Sternberg and Philip W. Gold

The Authors

ESTHER M. STERNBERG and PHILIP W. GOLD carry out their research on stress and immune systems at the National Institute of Mental Health, where Sternberg is chief of the section on neuroendocrinology and behavior and Gold is chief of the clinical neuroendocrinology branch. Sternberg received her M.D. from McGill University. Her work on the mechanisms and molecular basis of neuroimmune communication has led to a growing recognition of the importance of the mind-body interaction. She also is an authority on the L-tryptophan eosinophilia myalgia syndrome, which reached almost epidemic proportions in 1989. Prior to joining the NIMH in 1974, Gold received his medical training at Duke University and Harvard University. Gold and his group were among the first to introduce data implicating corticotropin-releasing hormone and its related hormones in the pathophysiology of melancholic and atypical depression and in the mechanisms of action of antidepressant drugs.

Immune response can be altered at the cellular level by stress hormones.



The belief that the mind plays an important role in physical illness goes back to the earliest days of medicine. From the time of the ancient Greeks to the beginning of the 20th century, it was generally accepted by both physician and patient that the mind can affect the course of illness, and it seemed natural to apply this concept in medical treatments of disease. After the discovery of antibiotics, a new assumption arose that treatment of infectious or inflammatory disease requires only the elimination of the foreign organism or agent that triggers the illness. In the rush to discover new antibiotics and drugs that cure specific infections and diseases, the fact that the body's own responses can influence susceptibility to disease and its course was largely ignored by medical researchers.

It is ironic that research into infectious and inflammatory disease first led 20th-century medicine to reject the idea that the mind influences physical illness, and now research in the same field—including the work of our laboratory and of our collaborators at the National Institutes of Health—is proving the contrary. New molecular and pharmacological tools have made it possible for us to identify the intricate network that exists between the immune system and the brain, a network that allows the two systems to signal each other continuously and rapidly. Chemicals produced by immune cells signal the brain, and the brain in turn sends chemical signals to restrain the immune system. These same chemical signals also affect behavior and the response to stress. Disruption of this communication network in any way, whether inherited or through drugs, toxic substances or surgery, exacerbates the diseases that these systems guard against: infectious, inflammatory, autoimmune and associated mood disorders.

The clinical significance of these findings is likely to prove profound. They hold the promise of extending the range of therapeutic treatments available for various disorders, as drugs previously known to work primarily for nervous system problems are shown to be effective against immune maladies, and vice versa. They also help to substantiate the popularly held impression (still discounted in some medical circles) that our state of mind can influence how well we resist or recover from infectious or inflammatory diseases.

The brain's stress response system is activated in threatening situations. The immune system responds automatically to pathogens and foreign molecules. These two response systems are the body's principal means for maintaining an internal steady state called homeostasis. A substantial proportion of human cellular machinery is dedicated to maintaining it.

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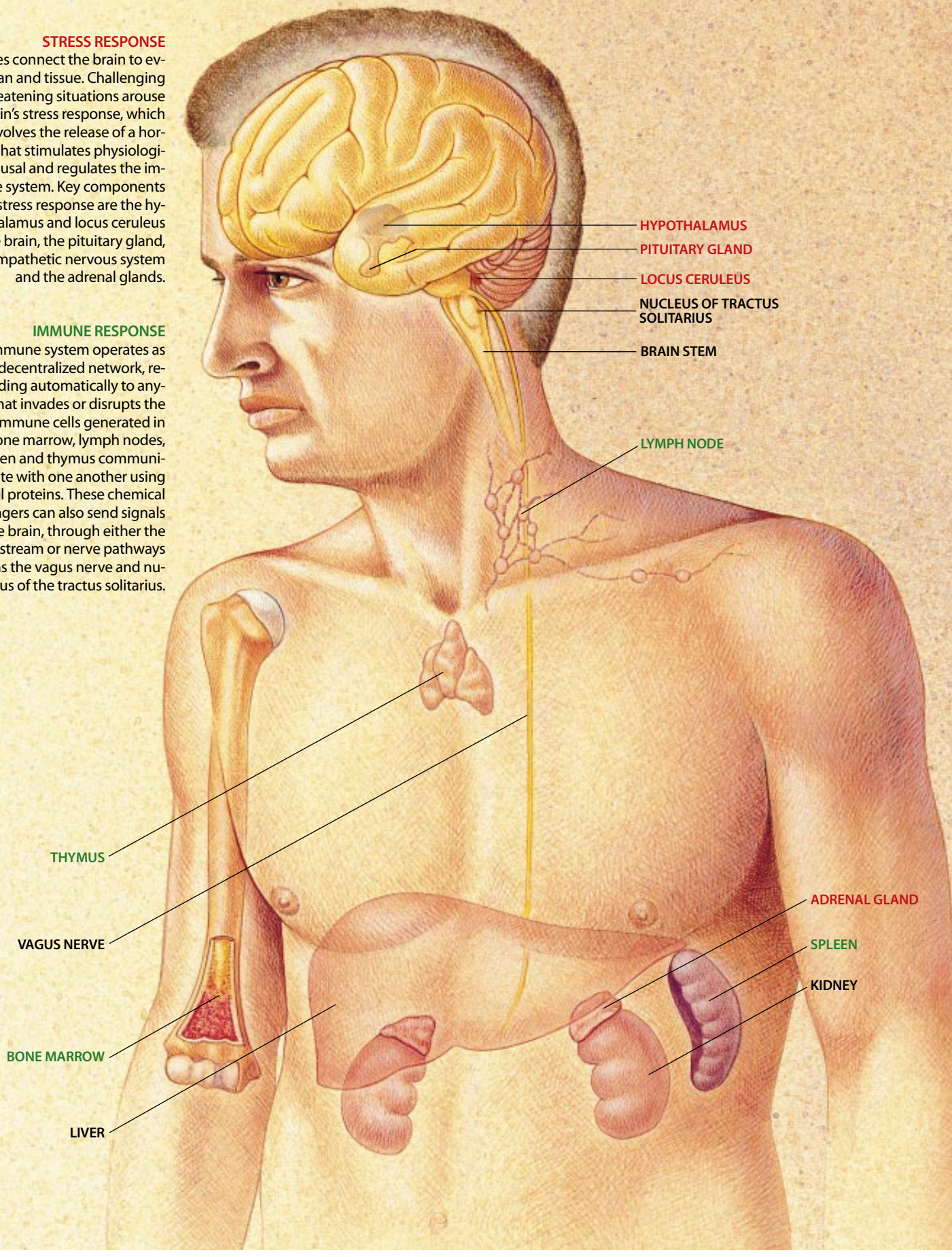
Anatomy of the Stress and Immune Systems

STRESS RESPONSE

Nerves connect the brain to every organ and tissue. Challenging or threatening situations arouse the brain's stress response, which involves the release of a hormone that stimulates physiological arousal and regulates the immune system. Key components in this stress response are the hypothalamus and locus ceruleus in the brain, the pituitary gland, the sympathetic nervous system and the adrenal glands.

IMMUNE RESPONSE

The immune system operates as a decentralized network, responding automatically to anything that invades or disrupts the body. Immune cells generated in the bone marrow, lymph nodes, spleen and thymus communicate with one another using small proteins. These chemical messengers can also send signals to the brain, through either the bloodstream or nerve pathways such as the vagus nerve and nucleus of the tractus solitarius.



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When homeostasis is disturbed or threatened, a repertoire of molecular, cellular and behavioral responses comes into play. These responses attempt to counteract the disturbing forces in order to reestablish a steady state. They can be specific to the foreign invader or a particular stress, or they can be generalized and nonspecific when the threat to homeostasis exceeds a certain threshold. The adaptive responses may themselves turn into stressors capable of producing disease. We are just beginning to understand the many ways in which the brain and the immune system are interdependent, how they help to regulate and counterregulate each other and how they themselves can malfunction and produce disease.

When we are facing a potentially life-threatening situation, the brain's stress response goes into action to enhance our focused attention, our fear and our fight-or-flight arousal, while inhibiting feeding, sex and sleep.

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The stress response promotes physiological and behavioral changes that enhance survival in threatening or taxing situations. For instance, when we are facing a potentially life-threatening situation, the brain's stress response goes into action to enhance our focused attention, our fear and our fight-or-flight response, while simultaneously inhibiting behaviors, such as feeding, sex and sleep, that might lessen the chance of immediate survival. The stress response, however, must be regulated to be neither excessive nor suboptimal; otherwise, disorders of arousal, thought and feeling emerge.

The immune system's job is to bar foreign pathogens from the body and to recognize and destroy those that penetrate its shield. The immune system also must neutralize potentially dangerous toxins, facilitate repair of damaged or worn tissues, and dispose of abnormal cells. Its responses are so powerful that they require constant regulation to ensure that they are neither excessive nor indiscriminate and yet remain effective. When the immune system escapes regulation, autoimmune and inflammatory diseases or immune deficiency syndromes result.

The immune and central nervous systems appear, at first glance, to be organized in very different ways. The brain is usually regarded as a centralized command center, sending and receiving electrical signals along fixed pathways, much like a telephone network. In contrast, the immune system is decentralized, and its organs (spleen, lymph nodes, thymus and bone marrow) are located throughout the body. The classical view is that the immune system communicates by releasing immune cells into the bloodstream that float, like boats, to new locations to deliver their messages or to perform other functions.

The central nervous and immune systems, however, are in fact more similar than different in their modes of receiving, recognizing and integrating signals from the external environment and in their structural design for accomplishing these tasks. Both the central nervous system and the immune system possess "sensory" elements, which receive information from the environment and other parts of the body, and "motor" elements, which carry out an appropriate response.

Cross Communication

Both systems also rely on chemical mediators for communication. Electrical signals along nerve pathways, for instance, are converted to chemical signals at the synapses between neurons. The chemical messengers produced by immune cells communicate not only with other parts of the immune system but also with the brain and nerves, and chemicals released by nerve cells can act as signals to immune cells. Hormones from the body travel to the brain in the bloodstream, and the brain itself makes hormones. Indeed, the brain is perhaps the most prolific endocrine organ in the body and produces many hormones that act both on the brain and on tissues throughout the body.

A key hormone shared by the central nervous and immune systems is corticotropin-releasing hormone (CRH); produced in the hypothalamus and several other brain regions, it unites the stress and immune responses. The hypothalamus releases CRH into a specialized bloodstream circuit that conveys the hormone to the pituitary gland, which is just beneath the brain. CRH causes the pituitary to release adrenocorticotropin hormone (ACTH) into the bloodstream, which in turn stimulates the adrenal glands to produce cortisol, the best-known hormone of the stress response.

Cortisol is a steroid hormone that increases the rate and strength of heart contractions, sensitizes blood vessels to the actions of norepinephrine (an adrenalinelike hormone) and affects many metabolic functions—actions that help to prepare the body to meet a stressful situation. In addition, cortisol is a potent immunoregulator and anti-inflammatory agent. It plays a crucial role in preventing the immune system from overreacting to injuries and damaging tissues. Furthermore, cortisol inhibits the release of CRH by the hypothalamus—a simple feedback loop that keeps this component of the stress response under control. Thus, CRH and cortisol directly link the body's brain-regulated stress response and its immune response.

CRH-secreting neurons of the hypothalamus send fibers to regions in the brain stem that help to regulate the sympathetic nervous system, as well as to another brain stem area called the locus ceruleus. The sympathetic nervous system, which mobilizes the body during stress, also innervates immune organs, such as the thymus, lymph nodes and spleen, and helps to control inflammatory responses throughout the body. Stimulation of the locus ceruleus leads to behavioral arousal, fear and enhanced vigilance.

Perhaps even more important for the induction of fear-related behaviors is the amygdala, where inputs from the sensory regions of the brain are charged as stressful or not. CRH-secreting neurons in the central nucleus of the amygdala send fibers to the hypothalamus and the locus ceruleus, as well as to other parts of the brain stem. These CRH-secreting neurons are targets of messengers released by immune cells during an immune response. By recruiting the CRH-secreting neurons, the immune signals not only activate cortisol-mediated restraint of the immune response but also induce behaviors that assist in recovery from illness or injury.

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CRH-secreting neurons also have connections with hypothalamic regions that regulate food intake and reproductive behavior. In addition, there are other hormonal and nerve systems, such as the thyroid, growth and female sex hormones, and the sympathomedullary pathways, that influence brain–immune system interactions.

The Immune System's Signals

The immune response is an elegant and finely tuned cascade of cellular events aimed at ridding the body of foreign substances, bacteria and viruses.

One of the major discoveries of contemporary immunology is that white blood cells produce small proteins that indirectly coordinate the responses of other parts of the immune system to pathogens. For example, the protein interleukin-1 (IL-1) is made by a type of white blood cell called a monocyte or macrophage. IL-1 stimulates another type of white blood cell, the lymphocyte, to produce interleukin-2 (IL-2), which in turn induces lymphocytes to develop into mature immune cells. Some mature lymphocytes, called plasma cells, make antibodies that fight infection, whereas others, the cytotoxic lymphocytes, kill viruses directly. Other interleukins mediate the activation of immune cells that are involved in allergic reactions.

The interleukins were originally named to reflect what was considered to be their primary function: communication between ("inter-") the white blood cells ("leukins"). But it is now known that interleukins also act as chemical signals between immune cells and many other types of cells and organs, including parts of the brain, and so a new name—"cytokine"—has been coined. Cytokines are biological molecules that cells use to communicate. Each cytokine is a distinct protein molecule, encoded by a separate gene, that targets a particular cell type. A cytokine can either stimulate or inhibit a response depending on the presence of other cytokines or other stimuli and the current state of metabolic activity. This flexibility allows the immune system to take the most appropriate actions to stabilize the local cellular environment and to maintain homeostasis.

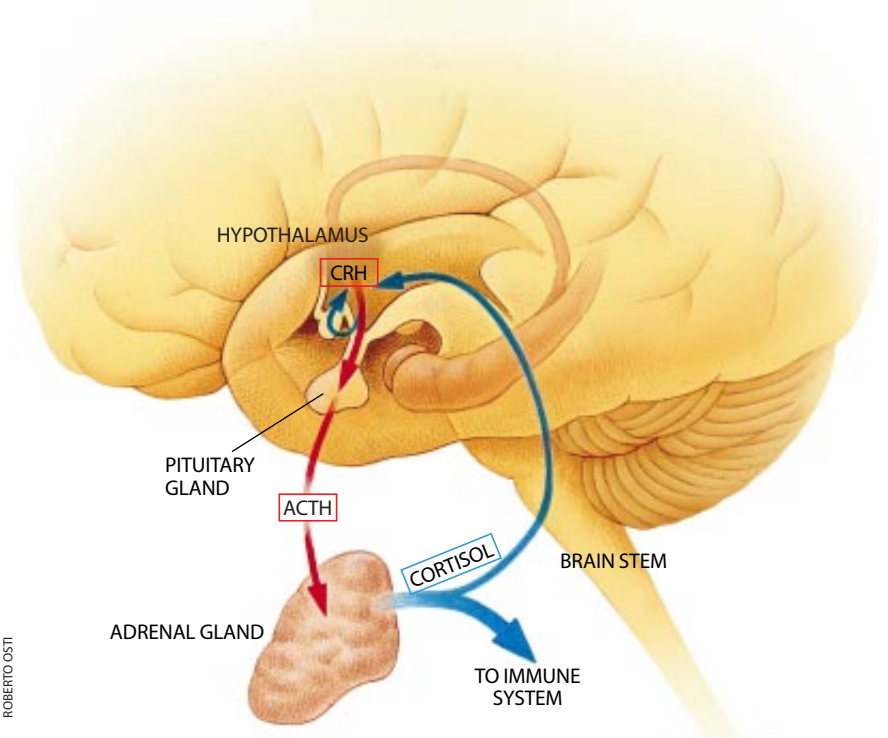
Cytokines from the body's immune system can send signals to the brain in several ways. Ordinarily, a "blood-brain barrier" shields the central nervous system from potentially dangerous molecules in the bloodstream. During inflammation or illness, however, this barrier becomes more permeable, and cytokines may be carried across into the brain with nutrients from the blood. Certain cytokines, on the other hand, readily pass through at any time. But cytokines do not have to cross the blood-brain barrier to exert their effects. Cytokines made in the lining of blood vessels in the brain can stimulate the release of secondary chemical signals in the brain tissue around the blood vessels.

Cytokines can also signal the brain via direct nerve routes, such as the vagus nerve, which innervates the heart, stomach, small intestine and other organs of the abdominal cavity. Injection of IL-1 into the abdominal cavity activates the nucleus of the tractus solitarius, the principal region of the brain stem for receipt of visceral sensory signals. Cutting the vagus nerve blocks activation of the tractus nucleus by IL-1. Sending signals along nerve routes is the most rapid mechanism—on the order of milliseconds—by which cytokines signal the brain.

Activation of the brain by cytokines from the peripheral parts of the body induces behaviors of the stress response, such as anxiety and cautious avoidance, that keep the affected individual out of harm's way until full healing occurs. Anyone who has experienced lethargy and excess sleepiness during an illness will recognize this set of characteristic responses as "sickness behavior."

Neurons and nonneuronal brain cells also produce cytokines of their own. Cytokines in the brain regulate nerve cell growth and death, and they also can be recruited by the immune system to stimulate the release of CRH. The IL-1 cytokine system in the brain is currently the best understood—all its components have been identified, including

Hypothalamus-Pituitary-Adrenal (HPA) Axis



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HPA AXIS is a central component of the brain's neuroendocrine response to stress. The hypothalamus, when stimulated, secretes corticotropin-releasing hormone (CRH) into the hypophyseal portal system, which supplies blood to the anterior pituitary. CRH stimulates the pituitary (*red arrows show stimulatory pathways*) to secrete adrenocorticotropin hormone (ACTH) into the bloodstream. ACTH causes the adrenal glands to release cortisol, the classic stress hormone that arouses the body to meet a challenging situation. But cortisol then modulates the stress response (*blue arrows indicate inhibitory effects*) by acting on the hypothalamus to inhibit the continued release of CRH. Also a potent immunoregulator, cortisol acts on many parts of the immune system to prevent it from overreacting and harming healthy cells and tissue.

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receptors and a naturally occurring antagonist that binds to IL-1 receptors without activating them. The anatomical and cellular locations of this IL-1 circuitry are being mapped out in detail, and this new knowledge will aid researchers in designing drugs that block or enhance the actions of such circuits and the functions they regulate.

Excessive amounts of cytokines in the brain can be toxic to nerves. In genetically engineered mice, transplanted genes that overexpress cytokines produce neurotoxic effects. Some of the neurological symptoms of AIDS in humans also may be caused by overexpression of certain cytokines in the brain. High levels of IL-1 and other cytokines have been found in the brain tissue of patients living with AIDS, concentrated in areas around the giant macrophages that invade the patients' brain tissue.

Any disruption of communication between the brain and the immune system leads to greater susceptibility to inflammatory disease and, frequently, to increased severity of the immune complications. For instance, animals whose brain-immune communications have been disrupted (through surgery or drugs) are highly liable to lethal complications of inflammatory diseases and infectious diseases.

Susceptibility to inflammatory disease that is associated with genetically impaired stress response can be found across species—in rats, mice, chickens and, though the evidence is less direct, humans. For instance, the Lewis strain of rat is naturally prone to many inflammatory diseases because of a severe impairment of its HPA axis, which greatly diminishes CRH secretion in response to stress. In contrast, the hyperresponsive HPA-axis in the Fischer strain of rat provides it with a strong resistance to inflammatory disease.

Evidence of a causal link between an impaired stress response and susceptibility to inflammatory disease comes from pharmacological and surgical studies. Pharmacological intervention such as treatment with a drug that blocks cortisol receptors enhances autoimmune inflammatory disease. Injecting low doses of cortisol into disease-susceptible rats enhances their resistance to inflammation. Strong evidence comes from surgical intervention. Removal of the pituitary gland or the adrenal glands from rats that normally are resistant to inflammatory disease renders them highly susceptible. Further proof comes from studies in which the transplantation of hypothalamic tissue from disease-resistant rats into the brain of susceptible rats dramatically improves their resistance to peripheral inflammation.

These animal studies demonstrate that disruption of the brain's stress response enhances the body's response to inflammatory disease, and reconstitution of the stress response reduces susceptibility to inflammation. One implication of these findings is that disruption of the brain-immune communication system by inflammatory, toxic or infectious agents could contribute to some of the variations in the course of the immune system's inflammatory response.

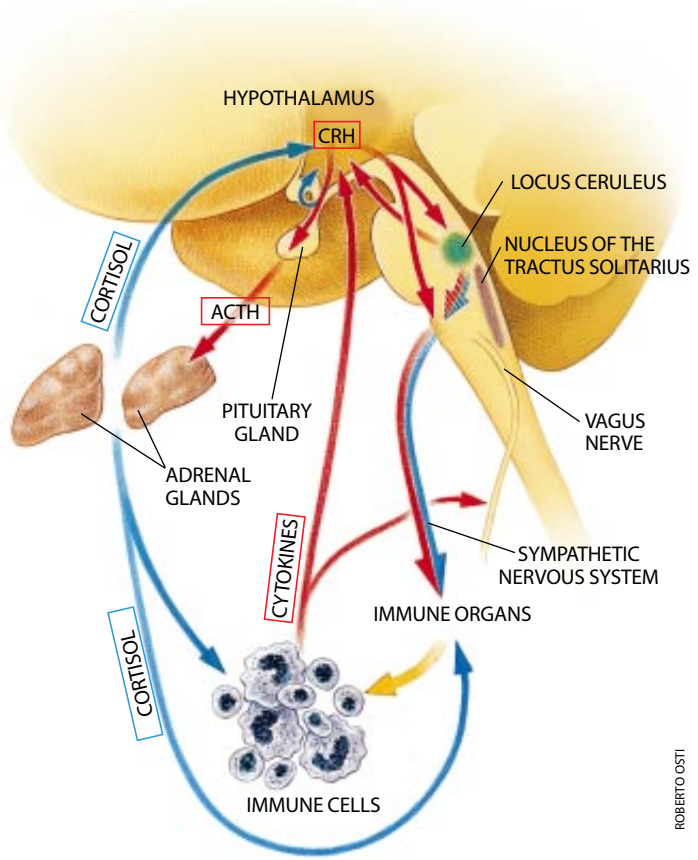
CRH and Depression

Although the role of the stress response in inflammatory disease in humans is more difficult to prove, there is a growing amount of evidence that a wide variety of such diseases are associated with impairment of the HPA axis and lower levels of CRH secretion, which ultimately results in a hyperactive immune system. Furthermore, patients with a mood disorder called atypical depression also have a blunted stress response and impaired CRH function, which leads to lethargy, fatigue, increased sleep and increased feeding that often produces weight gain.

Patients with other illnesses characterized by lethargy and fatigue, such as chronic fatigue syndrome, fibromyalgia and seasonal affective disorder (SAD), exhibit features of both depression and a hyperactive immune system. A person with chronic fatigue syndrome classically manifests debilitating lethargy or fatigue lasting six months or longer with no demonstrable medical cause, as well as feverishness, aches in joints and muscles, allergic symptoms and higher levels of antibodies to a variety of viral antigens (including Epstein-Barr virus).

Patients with fibromyalgia suffer from muscle aches, joint pains and sleep abnormalities, symptoms similar to early, mild rheumatoid arthritis. Both these illnesses are associated with a profound fatigue like that in atypical depression. SAD, which usually occurs in winter, is typified by lethargy, fatigue, increased food intake and increased sleep.

Interaction of the Brain and Immune System



BRAIN AND IMMUNE SYSTEM can either stimulate (*red arrows*) or inhibit (*blue arrows*) each other. Immune cells produce cytokines (chemical signals) that stimulate the hypothalamus through the bloodstream or via nerves elsewhere in the body. The hormone CRH, produced in the hypothalamus, activates the HPA axis. The release of cortisol tunes down the immune system. CRH, acting on the brain stem, stimulates the sympathetic nervous system, which innervates immune organs and regulates inflammatory responses throughout the body. Disruption of these communications in any way leads to greater susceptibility to disease and immune complications.

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Many of its symptoms are similar to those of atypical depression.

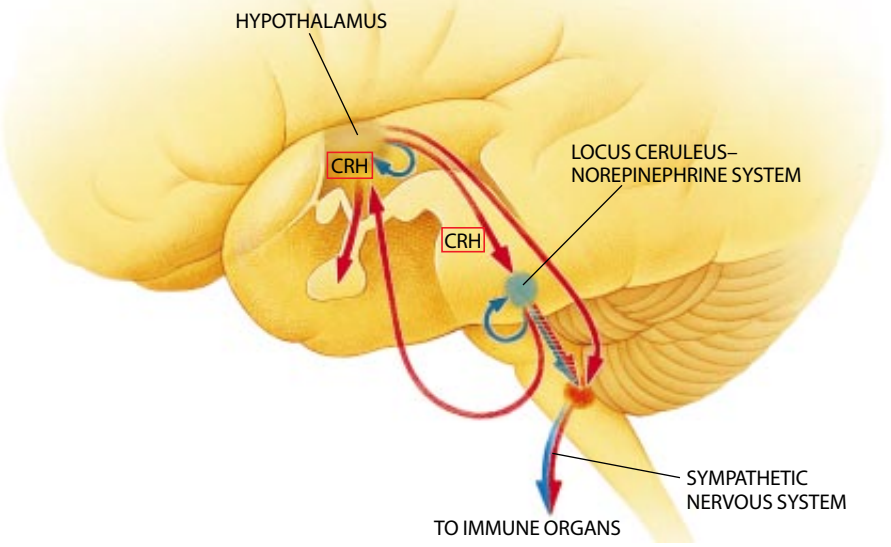
A deficiency of CRH could contribute to lethargy in patients with chronic fatigue syndrome. Injection of CRH into patients with fatigue syndrome causes a delayed and blunted ACTH secretion by the HPA axis. That same response is also seen in patients whose hypothalamus has been injured or who have a tumor. Also, fatigue and hyperactivity of the immune response are associated with cortisol deficiency, which occurs when CRH secretion decreases. The hormone levels and responses in patients with fatigue syndromes suggest—but do not prove—that their HPA-axis functions are impaired, resulting in a decrease in CRH and cortisol secretion and an increase in immune system activity. Together these findings suggest that human illness characterized by fatigue and hyperimmunity could possibly be treated by drugs that mimic CRH actions in the brain.

In contrast, the classic form of depression, melancholia, actually is not a state of inactivation and suppression of thought and feeling; rather it presents as an organized state of anxiety. The anxiety of melancholia is chiefly about the self. Melancholic patients feel impoverished and defective and often express hopelessness about the prospects for their unworthy selves in either love or work. The anxious hyperarousal of melancholic patients also manifests as a pervasive sense of vulnerability, and melancholic patients often interpret relatively neutral cues as harbingers of abandonment or embarrassment.

Melancholic patients also show behavioral alterations suggestive of physiological hyperarousal. They characteristically suffer from insomnia (usually early-morning awakening) and experience inhibition of eating, sexual activity and menstruation. One of the most widely found biological abnormalities in patients with melancholia is that of sustained hypersecretion of cortisol.

Many studies have been conducted on patients with major depression to determine whether the excessive level of cortisol associated with depression correlates with suppressed immune responses. Some have found a correlation between hypercortisolism and immunosuppression; others have not. Because depression can have a variety of mental and biochemical causes only some depressed patients may be immunosuppressed.

CRH, the Locus Ceruleus and Sympathetic Nervous System



ROBERTO OSTI

HYPOTHALAMIC CRH produces changes important to stress and inflammation adaptation in ways other than inducing cortisol release from the adrenal glands. Pathways from CRH-secreting neurons in the hypothalamus extend to the locus ceruleus in the brain stem. Separate pathways from other hypothalamic neurons to the brain stem influence sympathetic nervous system activity, which modulates inflammatory responses as well as regulating metabolic and cardiovascular activities. Stimulation by CRH of the locus ceruleus produces protective behaviors such as arousal and fear (*red indicates stimulation, blue inhibition*). The locus ceruleus, in turn, provides feedback to the hypothalamus for continued production of CRH and also acts on the sympathetic nervous system. Self-inhibitory feedback keeps the activities of CRH and the locus ceruleus under control.

The excessive secretion of cortisol in melancholic patients is the result predominantly of hypersecretion of CRH, caused by a defect in or above the hypothalamus. Thus, the clinical and biochemical manifestations of melancholia reflect a generalized stress response that has escaped the usual counterregulation, remaining, as it were, stuck in the "on" position.

The effects of tricyclic antidepressant drugs on components of the stress response support the concept that melancholia is associated with a chronic stress response. In rats, regular, but not acute, administration of the tricyclic antidepressant imipramine significantly lowers the levels of CRH precursors in the hypothalamus. Imipramine given for two months to healthy persons with normal cortisol levels causes a gradual and sustained decrease in CRH secretion and other HPA-axis functions, indicating that down-regulation of important components of the stress response is an intrinsic effect of imipramine.

Depression is also associated with inflammatory disease. About 20 percent of patients with rheumatoid arthritis develop clinical depression at some point during the course of their arthritic disease. A questionnaire commonly used by clinicians to diagnose depression contains about a dozen questions that are almost always answered affirmatively by patients with arthritis.

Stress and Illness

In the past, the association between an inflammatory disease and stress was considered by doctors to be secondary to the chronic pain and debilitation of the disease. The recent discovery of the common underpinning of the immune and stress responses may provide an explanation of why a patient can be susceptible to both inflammatory disease and depression. The hormonal dysregulation that underlies both inflammatory disease and depression can lead to either illness, depending on whether the perturbing stimulus is pro-inflammato-

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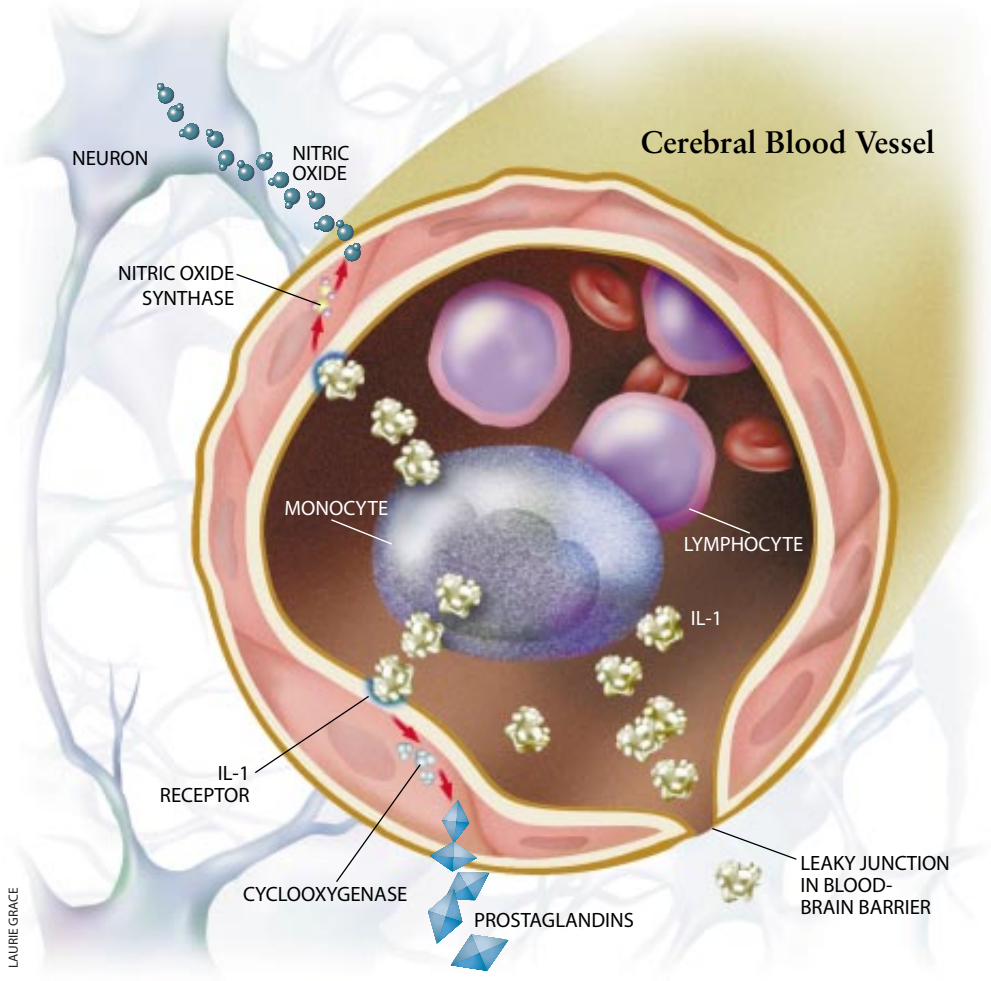

IMMUNE SIGNALS TO THE BRAIN via the bloodstream can occur directly or indirectly. Immune cells such as monocytes, a type of white blood cell, produce a chemical messenger called interleukin-1 (IL-1), which ordinarily will not pass through the blood-brain barrier. But certain cerebral blood vessels contain leaky junctions, which allow IL-1 molecules to pass into the brain. There they can activate the HPA axis and other neural systems. IL-1 also binds to receptors on the endothelial cells that line cerebral blood vessels. This binding can cause enzymes in the cells to produce nitric oxide or prostaglandins, which diffuse into the brain and act directly on neurons.

ry or psychologically stressful. That may explain why the waxing and waning of depression in arthritic patients does not always coincide with inflammatory flare-ups.

The popular belief that stress exacerbates inflammatory illness and that relaxation or removal of stress ameliorates it may indeed have a basis in fact. The interactions of the stress and immune systems and the hormonal responses they have in common could explain how conscious attempts to tone down responsivity to stress could affect immune responses.

How much of the responsivity to stress is genetically determined and how much can be consciously controlled is not known. The set point of the stress response is to some extent genetically determined. An event that is physiologically highly stressful to one individual may be much less so to another, depending on each person's genetic tendency to hormonal reactivity. The degree to which stress could precipitate or exacerbate inflammatory disease would then depend both on the intensity of the stressful stimulus and on the set point of the stress system.

Psychological stress can affect an individual's susceptibility to infectious diseases. The regulation of the immune system by the neurohormonal stress system provides a biological basis for understanding how stress might affect these diseases. There is evidence that stress does affect human immune responses to viruses and bacteria. In studies with volunteers given a standard dose of the common cold virus (rhinovirus), individuals who are simultaneously exposed to stress show more viral particles and produce more mucus than do nonstressed individuals. Medical students receiving hepatitis vaccination during their final exams do not develop full protection against hepatitis. These findings have important implications for the scheduling of vaccinations. People who are vaccinated during periods of stress might be less likely to develop full antibody protection.

Animal studies provide further evidence that stress affects the course and severity of viral illness, bacterial disease and septic shock. Stress in mice worsens the severity of influenza infection and affects both the HPA axis and the sympathetic nervous system. Animal studies suggest that neuroendocrine mechanisms could play a similar role in infections with other viruses, including HIV, and provide a mechanism for understanding clinical observations that stress may exacerbate the course of AIDS. Stress increases the susceptibility of mice to infection with mycobacteria, the bacteria that causes tuberculosis. It has been shown that an intact HPA axis protects rats against the lethal septic effects of salmonella bacteria. Finally, new understanding of interactions of the immune and stress responses can help explain the puzzling observation that classic psychological conditioning of animals can influence their immune responses. For example, working with rats, Robert Ader and Nicholas Cohen of the University of Rochester paired saccharin-flavored water with an immunosuppressive drug. Eventually the saccharin alone produced a decrease in immune function similar to that of the drug.

Stress is not only personal but is perceived through the prism of interactions with other persons. Social interactions can either add to or lessen psychological stress and similarly affect our hormonal responses to it, which in turn can alter immune responses. Thus, the social psychological stresses that we experience can affect our susceptibility to inflammatory and infectious diseases and the course of a disease. For instance, studies have shown that persons exposed to chronic social stresses for more than two months have increased susceptibility to the common cold.

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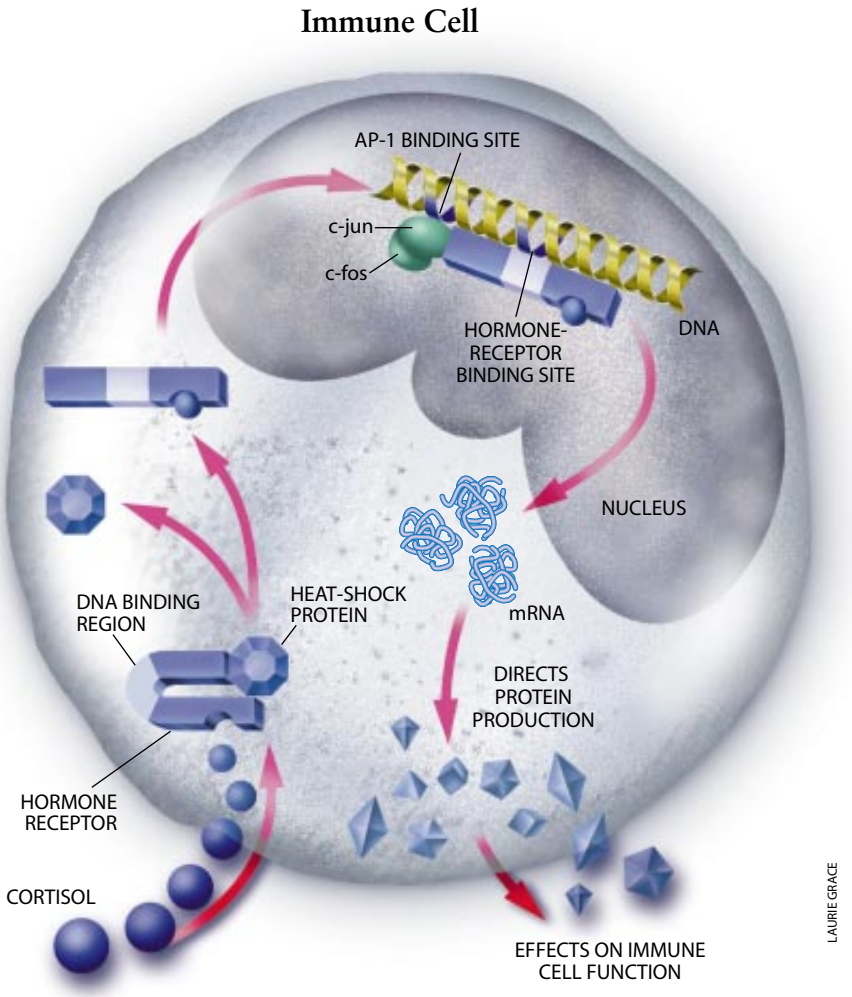
ALTERED GENETIC ACTIVITY in immune cells is an effect of cortisol. The cortisol receptors in immune cells are folded and bound to large "heat-shock" proteins. When cortisol enters a cell and binds to its receptor, the protein is displaced and the receptor unfolds. The receptor then binds to DNA in the nucleus, changing the cell's transcription of messenger RNA (mRNA) and production of proteins. (Other molecules called c-fos and c-jun bind with the receptor and confer more specificity on its action.) The proteins leave the cell and directly affect cytokine and lymphocyte production.



Other studies have shown that the immune responses of long-term caregivers, such as spouses of Alzheimer's patients, become blunted. Immune responses in unhappily married and divorcing couples are also blunted. Often the wife has a feeling of helplessness and experiences the greatest amount of stress. In such a scenario, studies have found that the levels of stress hormones are elevated and immune responses usually are lowered in the wife but not in the husband.

On the other hand, a positive supportive environment of extensive social networks or group psychotherapy can enhance immune response and resistance to disease—even cancer. Women with breast cancer, for instance, who receive strong, positive social support during their illness have significantly longer life spans than women without such support.

New Approaches to Treatment

For centuries, taking the cure at a mountain sanatorium or a hot-springs spa was the only available treatment for many chronic diseases. New understanding of the communication between the brain and immune system provides a physiological explanation of why such cures sometimes worked. Disruption of this communication network leads to an increase in susceptibility to disease and can worsen the course of the illness. Restoration of this communication system, whether through pharmacological agents or the relaxing effects of a spa, can be the first step on the road to recovery.

A corollary of these findings is that psychoactive drugs may in some cases be used to treat inflammatory diseases, and drugs that affect the immune system may be useful in treating some psychiatric disorders. There is growing evidence that our view of ourselves and others, our style of handling stresses, as well as our genetic makeup, can affect activities of the immune system. Similarly, there is good evidence that diseases associated with chronic inflammation significantly affect on one's mood or level of anxiety. Finally, these findings suggest that classification of illnesses into medical and psychiatric specialties, and the boundaries that have demarcated mind and body, are artificial. SA

Further Reading

NEURAL-IMMUNE INTERACTIONS. David L. Felton and Suzanne Y. Felton in *Encyclopedia of Human Biology*. Academic Press, 1991.

THE CONCEPTS OF STRESS AND STRESS SYSTEM DISORDERS. G. P. Chrousos and P. W. Gold in *Journal of the American Medical Association,* Vol. 267, No. 9, pages 1244–1252; March 4, 1992.

ENDOCRINE AND IMMUNE FUNCTION. J. K. Kiecolt-Glaser, W. Malarkey, J. T. Cacioppo and R. Glaser in *Handbook of Human Stress and Immunity*. Edited by R. Glaser and J. K. Kiecolt-Glaser. Academic Press, 1994.

STRESS: MECHANISMS AND CLINICAL IMPLICATIONS. G. P. Chrousos, R. McCarty, K. Pacak, G. Cizza, Esther M. Sternberg, Philip W. Gold and R. Kvetnansky in *Annals of the New York Academy of Sciences,* Vol. 771, 1995.

EMOTIONS AND DISEASE: FROM BALANCE OF HUMORS TO BALANCE OF MOLECULES. Esther M. Sternberg in *Nature Medicine,* Vol. 3, No. 3, pages 264–267; March 1997.

THE NEUROLOGIC BASIS OF FEVER. Clifford B. Saper and Christopher D. Breder in *New England Journal of Medicine,* Vol. 330, No. 26, pages 1880–1886; June 30, 1997.

EMOTIONS AND DISEASE. Catalogue for an Exhibition at the National Library of Medicine and National Institutes of Health. Edited by Esther M. Sternberg and Elizabeth Fee. Friends of the National Library of Medicine, Bethesda Md. May 1997.

National Institutes of Health World Wide Web site for information on emotions and disease: http://ohrm.od.nih.gov/ose/snapshots/

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The Problem of Consciousness

It can now be approached by scientific investigation of the visual system. The solution will require a close collaboration among psychologists, neuroscientists and theorists

by Francis Crick and Christof Koch

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The overwhelming question in neurobiology today is the relation between the mind and the brain. Everyone agrees that what we know as mind is closely related to certain aspects of the behavior of the brain, not to the heart, as Aristotle thought. Its most mysterious aspect is consciousness or awareness, which can take many forms, from the experience of pain to self-consciousness. In the past the mind (or soul) was often regarded, as it was by Descartes, as something immaterial, separate from the brain but interacting with it in some way. A few neuroscientists, such as Sir John Eccles, still assert that the soul is distinct from the body. But most neuroscientists now believe that all aspects of mind, including its most puzzling attribute—consciousness or awareness—are likely to be explainable in a more materialistic way as the behavior of large sets of interacting neurons. As William James, the father of American psychology, said a century ago, consciousness is not a thing but a process.

Exactly what the process is, however, has yet to be discovered. For many years after James penned *The Principles of Psychology,* consciousness was a taboo concept in American psychology because of the dominance of the behaviorist movement. With the advent of cognitive science in the mid-1950s, it became possible once more for psychologists to consider mental processes as opposed to merely observing behavior. In spite of these changes, until recently most cognitive scientists ignored consciousness, as did almost all neuroscientists. The problem was felt to be either purely "philosophical" or too elusive to study experimentally. It would not have been easy for a neuroscientist to get a grant just to study consciousness.

In our opinion, such timidity is ridiculous, so a few years ago we began to think about how best to attack the problem scientifically. How to explain mental events as being caused by the firing of large sets of neurons? Although there are those who believe such an approach is hopeless, we feel it is not productive to worry too much over aspects of the problem that cannot be solved scientifically or, more precisely, cannot be solved solely by using existing scientific ideas. Radically new concepts may indeed be needed—recall the modifications of scientific thinking forced on us by quantum mechanics. The only sensible approach is to press the experimental attack until we are confronted with dilemmas that call for new ways of thinking.

There are many possible approaches to the problem of consciousness. Some psychologists feel that any satisfactory theory should try to explain as many aspects of consciousness as possible, including emotion, imagination, dreams, mystical experiences and so on. Although such an all-embracing theory will be necessary in the long run, we thought it wiser to begin with the particular aspect of consciousness that is likely to yield most easily. What this aspect may be is a matter of personal judgment. We selected the mammalian visual system because humans are very visual animals and because so much experimental and theoretical work has already been done on it.

It is not easy to grasp exactly what we need to explain, and it will take many careful experiments before visual consciousness can be described scientifically. We did

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VISUAL AWARENESS primarily involves seeing what is directly in front of you, but it can be influenced by a three-dimensional representation of the object in view retained by the brain. If you see the back of a person's head, the brain infers that there is a face on the front of it. We know this is true because we would be very startled if a mirror revealed that the front was exactly like the back, as in this painting, *Reproduction Prohibited* (1937), by René Magritte.

The Authors

FRANCIS CRICK and CHRISTOF KOCH share an interest in the experimental study of consciousness. Crick is the co-discoverer, with James Watson, of the double helical structure of DNA. While at the Medical Research Council Laboratory of Molecular Biology in Cambridge, he worked on the genetic code and on developmental biology. Since 1976, he has been at the Salk Institute for Biological Studies in San Diego. His main interest lies in understanding the visual system of mammals. Koch was awarded his Ph.D. in biophysics by the University of Tübingen. After spending four years at the Massachusetts Institute of Technology, he joined the California Institute of Technology, where he is now professor of computation and neural systems. He is studying how single brain cells process information and the neural basis of motion perception, visual attention and awareness. He also designs analog VLSI vision chips for intelligent systems.

Lewis Carroll's vanishing cat can be used to study awareness.

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not attempt to define consciousness itself because of the dangers of premature definition. (If this seems like a copout, try defining the word "gene"—you will not find it easy.) Yet the experimental evidence that already exists provides enough of a glimpse of the nature of visual consciousness to guide research. In this article, we will attempt to show how this evidence opens the way to attack this profound and intriguing problem.

Visual theorists agree that the problem of visual consciousness is ill posed. The mathematical term "ill posed" means that additional constraints are needed to solve the problem. Although the main function of the visual system is to perceive objects and events in the world around us, the information available to our eyes is not sufficient by itself to provide the brain with its unique interpretation of the visual world. The brain must use past experience (either its own or that of our distant ancestors, which is embedded in our genes) to help interpret the information coming into our eyes. An example would be the derivation of the three-dimensional representation of the world from the two-dimensional signals falling onto the retinas of our two eyes or even onto one of them.

Visual theorists also would agree that seeing is a constructive process, one in which the brain has to carry out complex activities (sometimes called computations) in order to decide which interpretation to adopt of the ambiguous visual input. "Computation" implies that the brain acts to form a symbolic representation of the visual world, with a mapping (in the mathematical sense) of certain aspects of that world onto elements in the brain.

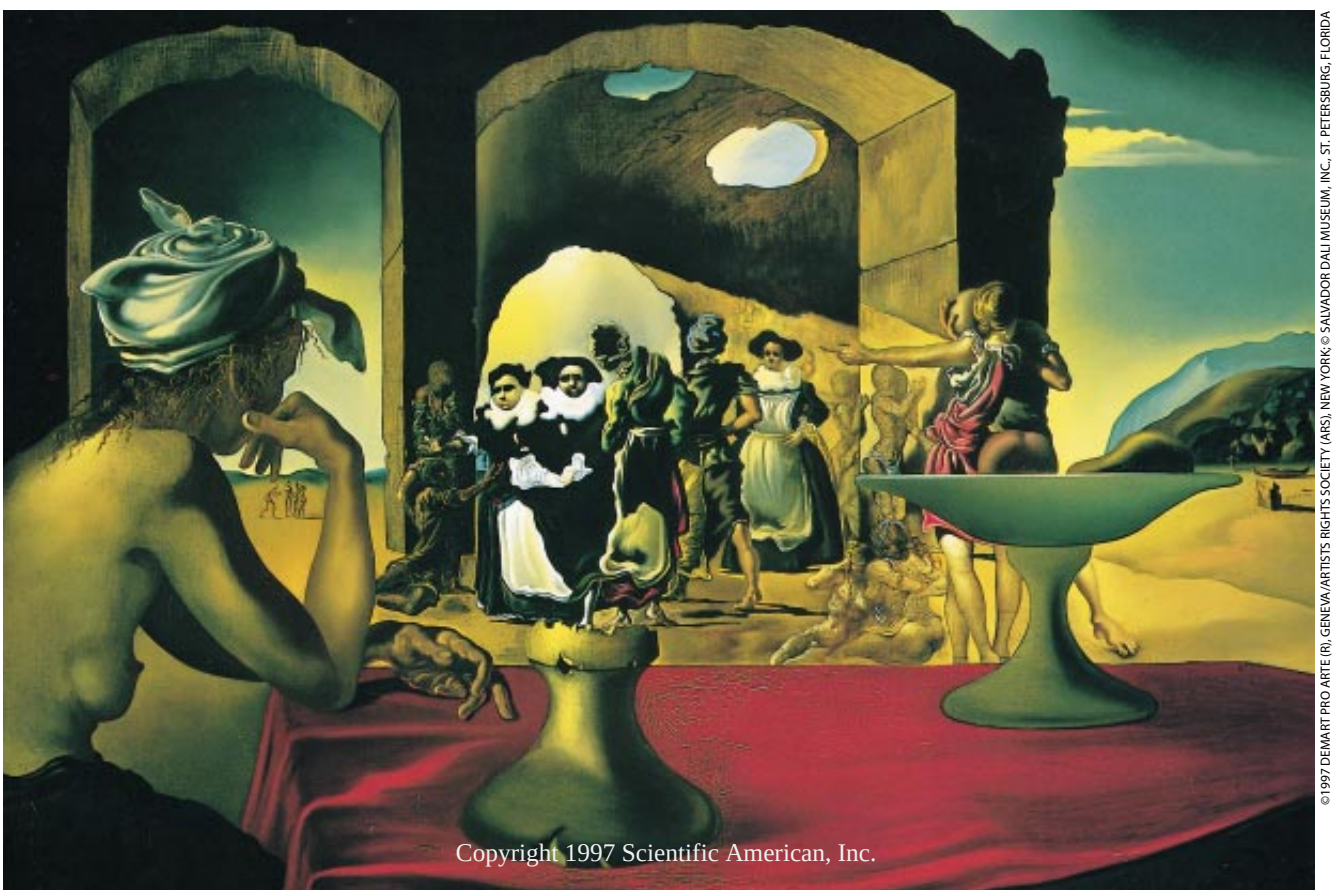
Ray Jackendoff of Brandeis University postulates, as do most cognitive scientists, that the computations carried out by the brain are largely unconscious and that what we become aware of is the result of these computations. But while the customary view is that this awareness occurs at the highest levels of the computational system, Jackendoff has proposed an intermediate-level theory of consciousness.

What we see, Jackendoff suggests, relates to a representation of surfaces that are directly visible to us, together with their outline, orientation, color, texture and movement. (This idea has similarities to what the late David C. Marr of the Massachusetts Institute of Technology called a "2 $^1/_2$-dimensional sketch." It is more than a two-dimensional sketch because it conveys the orientation of the visible surfaces. It is less than three-dimensional because depth information is not explicitly represented.) In the next stage this sketch is processed by the brain to produce a three-dimensional representation. Jackendoff argues that we are not visually aware of this three-dimensional representation.

An example may make this process clearer. If you look at a person whose back is turned to you, you can see the back of the head but not the face. Nevertheless, your brain infers that the person has a face. We can deduce as much because if that person turned around and had no face, you would be very surprised.

The viewer-centered representation that corresponds to the visible back of the head is what you are vividly aware of. What your brain infers about the front would come from some kind of three-dimensional representation. This does not mean that information flows only from the surface representation to the three-dimensional one; it almost certainly flows in both directions.

AMBIGUOUS IMAGES were frequently used by Salvador Dali in his paintings. In *Slave Market with the Disappearing Bust of Voltaire* (1940), the bust of the French philosopher Voltaire is apparent from a distance but transforms into figures of three people when viewed at close range. Studies with ambiguous figures in the behaving monkey have found that many neurons in higher cortical areas respond only to the currently "perceived" figure; the neuronal response to the "unseen" image is suppressed.



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When you imagine the front of the face, what you are aware of is a surface representation generated by information from the three-dimensional model.

It is important to distinguish between an explicit and an implicit representation. An explicit representation is something that is symbolized without further processing. An implicit representation contains the same information but requires further processing to make it explicit. The pattern of colored dots on a television screen, for example, contains an implicit representation of objects (say, a person's face), but only the dots and their locations are explicit. When you see a face on the screen, there must be neurons in your brain whose firing, in some sense, symbolizes that face.

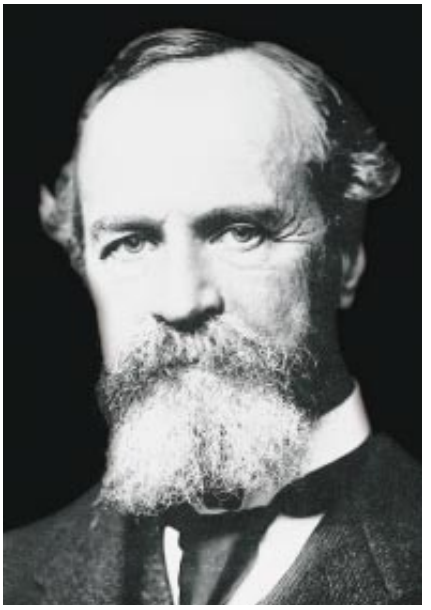
We call this pattern of firing neurons an active representation. A latent representation of a face must also be stored in the brain, probably as a special pattern of synaptic connections between neurons. For example, you probably have a representation of the Statue of Liberty in your brain, a representation that usually is inactive. If you do think about the Statue, the representation becomes active, with the relevant neurons firing away.

An object, incidentally, may be represented in more than one way—as a visual image, as a set of words and their related sounds, or even as a touch or a smell. These different representations are likely to interact with one another. The representation is likely to be distributed over many neurons, both locally and more globally. Such a representation may not be as simple and straightforward as uncritical introspection might indicate. There is suggestive evidence, partly from studying how neurons fire in various parts of a monkey's brain and partly from examining the effects of certain types of brain damage in humans, that different aspects of a face—and of the implications of a face—may be represented in different parts of the brain.

First, there is the representation of a face as a face: two eyes, a nose, a mouth and so on. The neurons involved are usually not too fussy about the exact size or position of this face in the visual field, nor are they very sensitive to small changes in its orientation. In monkeys, there are neurons that respond best when the face is turning in a particular direction, while others seem to be more concerned with the direction in which the eyes are gazing.

Then there are representations of the parts of a face, as separate from those for the face as a whole. Further, the implications of seeing a face, such as that person's sex, the facial expression, the familiarity or unfamiliarity of the face, and in particular whose face it is, may each be correlated with neurons firing in other places.

What we are aware of at any moment, in one sense or another, is not a simple matter. We have suggested that there may be a very transient form of fleeting awareness that represents only rather simple features and does not require an attentional mechanism. From this brief awareness the brain constructs a viewer-centered representation—what we see vividly and clearly—that does require attention. This in turn probably leads to three-dimensional object representations and thence to more cognitive ones.



BETTMANN ARCHIVE

WILLIAM JAMES, the father of American psychology, observed that consciousness is not a thing but a process.

Representations corresponding to vivid consciousness are likely to have special properties. William James thought that consciousness involved both attention and short-term memory. Most psychologists today would agree with this view. Jackendoff writes that consciousness is "enriched" by attention, implying that whereas attention may not be essential for certain limited types of consciousness, it is necessary for full consciousness. Yet it is not clear exactly which forms of memory are involved. Is long-term memory needed? Some forms of acquired knowledge are so embedded in the machinery of neural processing that they are almost certainly used in becoming aware of something. On the other hand, there is evidence from studies of brain-damaged patients that the ability to lay down new long-term episodic memories is not essential for consciousness to be experienced.

It is difficult to imagine that anyone could be conscious if he or she had no memory whatsoever of what had just happened, even an extremely short one. Visual psychologists talk of iconic memory, which lasts for a fraction of a second, and working memory (such as that used to remember a new telephone number) that lasts for only a few seconds unless it is rehearsed. It is not clear whether both of these are essential for consciousness. In any case, the division of short-term memory into these two categories may be too crude.

If these complex processes of visual awareness are localized in parts of the brain, which processes are likely to be where? Many regions of the brain may be involved, but it is almost certain that the cerebral neocortex plays a dominant role. Visual information from the retina reaches the neocortex mainly by way of a part of the thalamus (the lateral geniculate nucleus); another significant visual pathway from the retina is to the superior colliculus, at the top of the brain stem.

The cortex in humans consists of two intricately folded sheets of nerve tissue, one on each side of the head. These sheets are connected by a large tract of about half a billion axons called the corpus callosum. It is well known that if the corpus callosum is cut, as is done for certain cases of intractable epilepsy, one side of the brain is not aware of what the other side is seeing. In particular, the left side of the brain (in a right-handed person) appears not to be aware of visual information received exclusively by the right side. This shows that none of the information required for visual awareness can reach the other side of the brain by traveling down to the brain stem and, from there, back up. In a normal person, such information can get to the other side only by using the axons in the corpus callosum.

A different part of the brain—the hippocampal system—is involved in one-shot, or episodic, memories that, over weeks and months, it passes on to the neocortex. This system is so placed that it receives inputs from, and projects to, many parts of the brain. Thus, one might suspect that the hippocampal system is

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the essential seat of consciousness. This is not the case: evidence from studies of patients with damaged brains shows that this system is not essential for visual awareness, although naturally a patient lacking one is severely handicapped in everyday life because he cannot remember anything that took place more than a minute or so in the past.

In broad terms, the neocortex of alert animals probably acts in two ways. By building on crude and somewhat redundant wiring, produced by our genes and by embryonic processes, the neocortex draws on visual and other experience to slowly "rewire" itself to create categories (or "features") it can respond to. A new category is not fully created in the neocortex after exposure to only one example of it, although some small modifications of the neural connections may be made.

The second function of the neocortex (at least of the visual part of it) is to respond extremely rapidly to incoming signals. To do so, it uses the categories it has learned and tries to find the combinations of active neurons that, on the basis of its past experience, are most likely to represent the relevant objects and events in the visual world at that moment. The formation of such coalitions of active neurons may also be influenced by biases coming from other parts of the brain: for example, signals telling it what best to attend to or high-level expectations about the nature of the stimulus.

Consciousness, as James noted, is always changing. These rapidly formed coalitions occur at different levels and interact to form even broader coalitions. They are transient, lasting usually for only a fraction of a second. Because coalitions in the visual system are the basis of what we see, evolution has seen to it that they form as fast as possible; otherwise, no animal could survive. The brain is handicapped in forming neuronal coalitions rapidly because, by computer standards, neurons act very slowly. The brain compensates for this relative slowness partly by using very many neurons, simultaneously and in parallel, and partly by arranging the system in a roughly hierarchical manner.

If visual awareness at any moment corresponds to sets of neurons firing, then the obvious question is: Where are these neurons located in the brain, and in what way are they firing? Visual awareness is highly unlikely to occupy all the neurons in the neocortex that are firing above their background rate at a particular moment. We would expect that, theoretically, at least some of these neurons would be involved in doing computations—trying to arrive at the best coalitions—whereas others would express the results of these computations, in other words, what we see.

Fortunately, some experimental evidence can be found to back up this theoretical conclusion. A phenomenon called binocular rivalry may help identify the neurons whose firing symbolizes awareness. This phenomenon can be seen in dramatic form in an exhibit prepared by Sally Duensing and Bob Miller at the Exploratorium in San Francisco.

Conflicting Inputs

Binocular rivalry occurs when each eye has a different visual input relating to the same part of the visual field. The early visual system on the left side of the brain receives an input from both eyes but sees only the part of the visual field to the right of the fixation point. The converse is true for the right side. If these two conflicting inputs are rivalrous, one sees not the two inputs superimposed but first one input, then the other, and so on in alternation.

In the exhibit, called "The Cheshire Cat," viewers put their heads in a fixed place and are told to keep the gaze fixed. By means of a suitably placed mirror, one of the eyes can look at another person's face, directly in front, while the other eye sees a blank white screen to the side. If the viewer waves a hand in front of this plain screen at the same location in his or her visual field occupied by the face, the face is wiped out. The movement of the hand, being visually very salient, has captured the brain's attention. Without attention the face cannot be seen. If the viewer moves the eyes, the face reappears.

In some cases, only part of the face disappears. Sometimes, for example, one eye, or both eyes, will remain. If the viewer looks at the smile on the person's face, the face may disappear, leaving only the smile. For this reason, the effect has been called the Cheshire Cat effect, after the cat in Lewis Carroll's *Alice's Adventures in Wonderland*.

Although it is very difficult to record activity in individual neurons in a human brain, such studies can be done in monkeys. A simple example of binocular rivalry has been studied in a monkey by Nikos K. Logothetis and Jeffrey D. Schall, both then at M.I.T. They

The Cheshire Cat Experiment

This simple experiment with a mirror illustrates one aspect of visual awareness. It relies on a phenomenon called binocular rivalry, which occurs when each eye has a different input from the same part of the visual field. Motion in the field of one eye can cause either the entire image or parts of the image to be erased. The movement captures the brain's attention.

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trained a macaque to keep its eyes still and to signal whether it is seeing upward or downward movement of a horizontal grating. To produce rivalry, upward movement is projected into one of the monkey's eyes and downward movement into the other, so that the two images overlap in the visual field. The monkey signals that it sees up and down movements alternatively, just as humans would. Even though the motion stimulus coming into the monkey's eyes is always the same, the monkey's percept changes every second or so.

Cortical area MT (which some researchers prefer to label V5) is an area mainly concerned with movement. What do the neurons in MT do when the monkey's percept is sometimes up and sometimes down? (The researchers studied only the monkey's first response.) The simplified answer—the actual data are rather more messy—is that whereas the firing of some of the neurons correlates with the changes in the percept, for others the average firing rate is relatively unchanged and independent of which direction of movement the monkey is seeing at that moment. Thus, it is unlikely that the firing of all the neurons in the visual neocortex at one particular moment corresponds to the monkey's visual awareness. Exactly which neurons do correspond to awareness remains to be discovered.

We have postulated that when we clearly see something, there must be neurons actively firing that stand for what we see. This might be called the activity principle. Here, too, there is some experimental evidence. One example is the firing of neurons in a specific cortical visual area in response to illusory contours. Another and perhaps more striking case is the filling in of the blind spot. The blind spot in each eye is caused by the lack of photoreceptors in the area of the retina where the optic nerve leaves the retina and projects to the brain. Its location is about 15 degrees from the fovea (the visual center of the eye). Yet if you close one eye, you do not see a hole in your visual field.

Philosopher Daniel C. Dennett of Tufts University is unusual among philosophers in that he is interested both in psychology and in the brain. This interest is much to be welcomed. In a recent book, *Consciousness Explained*, he has argued that it is wrong to talk about filling in. He concludes, correctly, that "an absence of information is not the same as information about an absence." From this general principle he argues that the brain does not fill in the blind spot but rather ignores it.

Dennett's argument by itself, however, does not establish that filling in does not occur; it only suggests that it might not. Dennett also states that "your brain has no machinery for [filling in] at this location." This statement is incorrect. The primary visual cortex lacks a direct input from one eye, but normal "machinery" is there to deal with the input from the other eye. Ricardo Gattass and his colleagues at the Federal University of Rio de Janeiro have shown that in the macaque some of the neurons in the blind-spot area of the primary visual cortex do respond to input from both eyes, probably assisted by inputs from other parts of the cortex. Moreover, in the case of simple filling in, some of the neurons in that region respond as if they were actively filling in.

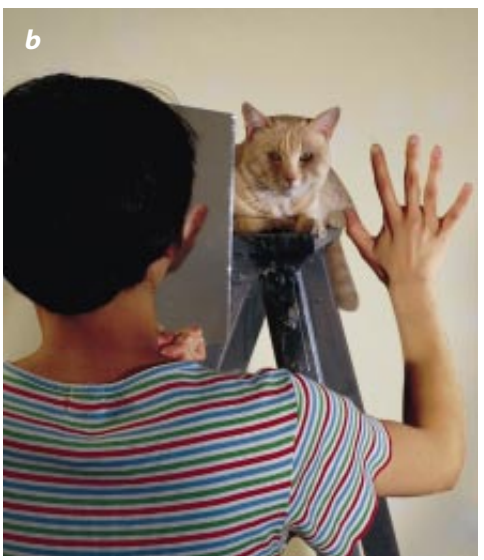
Thus, Dennett's claim about blind spots is incorrect. In addition, psychological experiments by Vilayanur S. Ramachandran [see "Blind Spots," Scientific American, May 1992] have shown that what is filled in can be quite complex depending on the overall context of the visual scene. How, he argues, can your brain be ignoring something that is in fact commanding attention?

Filling in, therefore, is not to be dismissed as nonexistent or unusual. It probably represents a basic interpolation process that can occur at many levels in the neocortex. It is, incidentally, a good example of what is meant by a constructive process.

How can we discover the neurons whose firing symbolizes a particular percept? William T. Newsome and his colleagues at Stanford University have done a series of brilliant experiments on neurons in cortical area MT of the macaque's brain. By studying a neuron in area MT, we may discover that it responds best to very specific visual features having to do with motion. A neuron, for instance, might fire strongly in response to the movement of a bar in a particular place in the visual field, but only when the bar is oriented at a certain angle, moving in one of the two directions perpendicular to its length within a certain range of speed.

It is technically difficult to excite just a single neuron, but it is known that neurons that respond to roughly the same position, orientation and direction of movement of a bar tend to be located near one another in the cortical sheet. The experimenters taught the monkey a

To observe the effect, a viewer divides the field of vision with a mirror placed between the eyes (*a*). One eye sees the cat; the other eye a reflection in the mirror of a white wall or background. The viewer then waves the hand that corresponds to the eye looking at the mirror so that the hand passes through the area in which the image of the cat appears in the other eye (*b*). The result is that the cat may disappear. Or if the viewer was attentive to a specific feature before the hand was waved, those parts—the eyes or even a mocking smile—may remain (*c*). —*F.C. and C.K.*



PHOTOGRAPHS BY JASON GOLTZ

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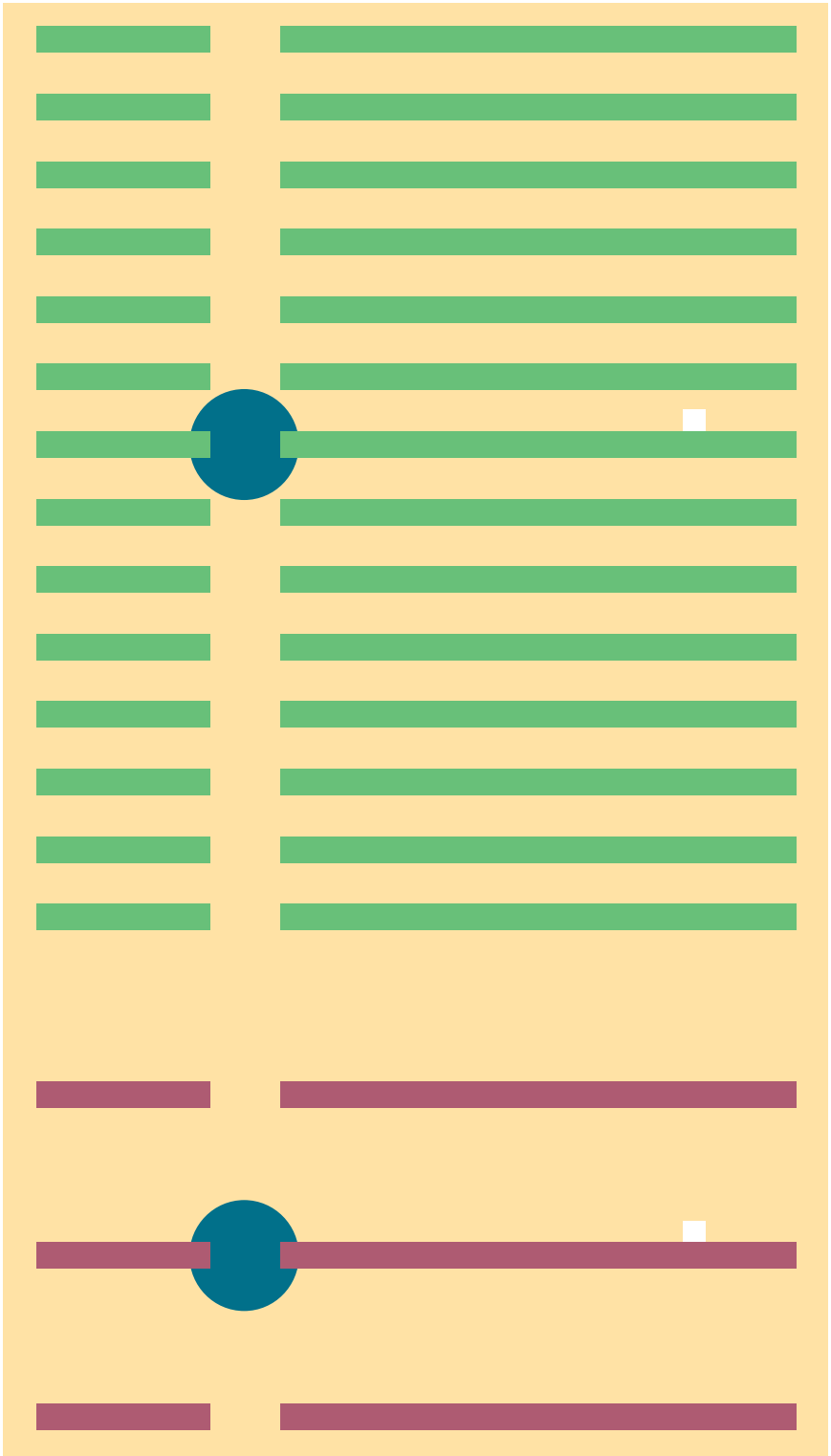

JOHNNY JOHNSON

OPTICAL ILLUSION devised by Vilayanur S. Ramachandran illustrates the brain's ability to fill in, or construct, visual information that is missing because it falls on the blind spot of the eye. When you look at the patterns of broken green bars, the visual system produces two illusory contours defining a vertical strip. Now shut your right eye and focus on the white square in the green series of bars. Move the page toward your eye until the blue dot disappears (roughly six inches in front of your nose). Most observers report seeing the vertical strip completed across the blind spot, not the broken line. Try the same experiment with the series of just three red bars. The illusory vertical contours are less well defined, and the visual system tends to fill in the horizontal bar across the blind spot. Thus, the brain fills in differently depending on the overall context of the image.

simple task in movement discrimination using a mixture of dots, some moving randomly, the rest all in one direction. They showed that electrical stimulation of a small region in the right place in cortical area MT would bias the monkey's motion discrimination, almost always in the expected direction.

Thus, the stimulation of these neurons can influence the monkey's behavior and probably its visual percept. Such experiments do not, however, show decisively that the firing of such neurons is the exact neural correlate of the percept. The correlate could be only a subset of the neurons being activated. Or perhaps the real correlate is the firing of neurons in another part of the visual hierarchy that are strongly influenced by the neurons activated in area MT.

These same reservations apply also to cases of binocular rivalry. Clearly, the problem of finding the neurons whose firing symbolizes a particular percept is not going to be easy. It will take many careful experiments to track them down even for one kind of percept.

It seems obvious that the purpose of vivid visual awareness is to feed into the cortical areas concerned with the implications of what we see; from there the information shuttles on the one hand to the hippocampal system, to be encoded (temporarily) into long-term episodic memory, and on the other to the planning levels of the motor system. But is it possible to go from a visual input to a behavioral output without any relevant visual awareness?

That such a process can happen is demonstrated by the remarkable class of patients with "blindsight." These patients, all of whom have suffered damage to their visual cortex, can point with fair accuracy at visual targets or track them with their eyes while vigorously denying seeing anything. In fact, these patients are as surprised as their doctors by their abilities. The amount of information that "gets through," however, is limited: blindsight patients have some ability to respond to wavelength, orientation and motion, yet they cannot distinguish a triangle from a square.

It is naturally of great interest to know which neural pathways are being used in these patients. Investigators originally suspected that the pathway ran through the superior colliculus. Recent experiments suggest that a direct albeit weak connection may be involved between the lateral geniculate nucleus and other visual areas in the cortex. It is unclear

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whether an intact primary visual cortex region is essential for immediate visual awareness. Conceivably the visual signal in blindsight is so weak that the neural activity cannot produce awareness, although it remains strong enough to get through to the motor system.

Normal-seeing people regularly respond to visual signals without being fully aware of them. In automatic actions, such as swimming or driving a car, complex but stereotypical actions occur with little, if any, associated visual awareness. In other cases, the information conveyed is either very limited or very attenuated. Thus, while we can function without visual awareness, our behavior without it is rather restricted.

Clearly, it takes a certain amount of time to experience a conscious percept. It is difficult to determine just how much time is needed for an episode of visual awareness, but one aspect of the problem that can be demonstrated experimentally is that signals received close together in time are treated by the brain as simultaneous.

A disk of red light is flashed for, say, 20 milliseconds, followed immediately by a 20-millisecond flash of green light in the same place. The subject reports that he did not see a red light followed by a green light. Instead he saw a yellow light, just as he would have if the red and the green light had been flashed simultaneously. Yet the subject could not have experienced yellow until after the information from the green flash had been processed and integrated with the preceding red one.

Experiments of this type led psychologist Robert Efron, now at the University of California at Davis, to conclude that the processing period for perception is about 60 to 70 milliseconds. Similar periods are found in experiments with tones in the auditory system. It is always possible, however, that the processing times may be different in higher parts of the visual hierarchy and in other parts of the brain. Processing is also more rapid in trained, compared with naive, observers.

Because it appears to be involved in some forms of visual awareness, it would help if we could discover the neural basis of attention. Eye movement is a form of attention, since the area of the visual field in which we see with high resolution is remarkably small, roughly the area of the thumbnail at arm's length. Thus, we move our eyes to gaze directly at an object in order to see it more clearly. Our eyes usually move three or four times a second. Psychologists have shown, however, that there appears to be a faster form of attention that moves around, in some sense, when our eyes are stationary.

The exact psychological nature of this faster attentional mechanism is at present controversial. Several neuroscientists, however, including Robert Desimone and his colleagues at the National Institute of Mental Health, have shown that the rate of firing of certain neurons in the macaque's visual system depends on what the monkey is attending to in the visual field. Thus, attention is not solely a psychological concept; it also has neural correlates that can be observed. A number of researchers have found that the pulvinar, a region of the thalamus, appears to be involved in visual attention. We would like to believe that the thalamus deserves to be called "the organ of attention," but this status has yet to be established.

Rhythmic and synchronized firing may be the neural correlate of awareness and might bind together activity [concerning the same object] in different cortical areas.

Attention and Awareness

The major problem is to find what activity in the brain corresponds directly to visual awareness. It has been speculated that each cortical area produces awareness of only those visual features that are "columnar," or arranged in the stack or column of neurons perpendicular to the cortical surface. Thus, the primary visual cortex could code for orientation and area MT for motion. So far experimentalists have not found one particular region in the brain where all the information needed for visual awareness appears to come together. Dennett has dubbed such a hypothetical place "The Cartesian Theater." He argues on theoretical grounds that it does not exist.

Awareness seems to be distributed not just on a local scale, but more widely over the neocortex. Vivid visual awareness is unlikely to be distributed over every cortical area because some areas show no response to visual signals. Awareness might, for example, be associated with only those areas that connect back directly to the primary visual cortex or alternatively with those areas that project into one another's layer 4. (The latter areas are always at the same level in the visual hierarchy.)

The key issue, then, is how the brain forms its global representations from visual signals. If attention is indeed crucial for visual awareness, the brain could form representations by attending to just one object at a time, rapidly moving from one object to the next. For example, the neurons representing all the different aspects of the attended object could all fire together very rapidly for a short period, possibly in rapid bursts.

This fast, simultaneous firing might not only excite those neurons that symbolized the implications of that object but also temporarily strengthen the relevant synapses so that this particular pattern of firing could be quickly recalled—a form of short-term memory. If only one representation needs to be held in short-term memory, as in remembering a single task, the neurons involved may continue to fire for a period.

A problem arises if it is necessary to be aware of more than one object at exactly the same time. If all the attributes of two or more objects were represented by neurons firing rapidly, their attributes might be confused. The color of one might become attached to the shape of another. This happens sometimes in very brief presentations.

Some time ago Christoph von der Malsburg, now at the Ruhr-Universität Bochum, suggested that this difficulty would be circumvented if the neurons associated with any one object all fired in synchrony (that is, if their times of firing were correlated) but out of synchrony with those representing other objects. Recently two groups in Germany reported that there does appear to be correlated firing between neurons in the visual cortex of the cat, often in a rhythmic manner, with a frequency in the 35- to 75-hertz range, sometimes called 40-hertz, or g, oscillation.

Von der Malsburg's proposal prompted us to suggest that this rhythmic and synchronized firing might be the neural correlate of awareness and that it might serve to bind together activity concerning the same object in different cortical areas. The matter is still undecided, but at present the fragmentary experimen-

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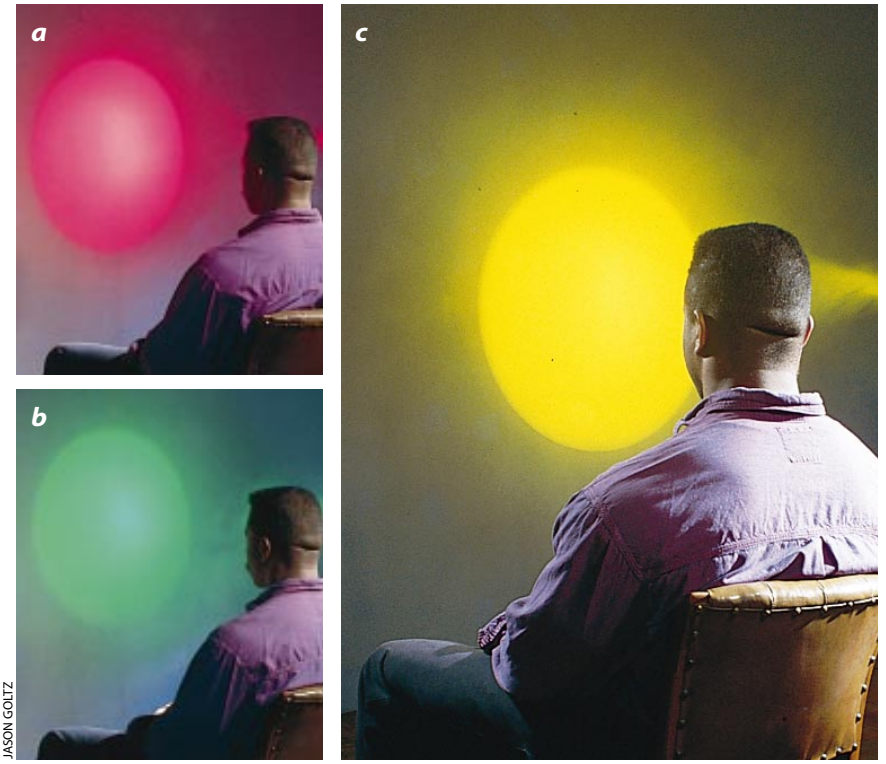

JASON GOLITZ

BRIEF FLASHES of colored light enable researchers to infer the minimum time required for visual awareness. A disk of red light is projected for 20 milliseconds (a), followed immediately by a 20-millisecond flash of green light (b). But the observer reports seeing a single flash of yellow (c), the color that would be apparent if red and green were projected simultaneously. The subject does not become aware of red followed by green until the length of the flashes is extended to 60 to 70 milliseconds.

tal evidence does rather little to support such an idea. Another possibility is that the 40-hertz oscillations may help distinguish figure from ground or assist the mechanism of attention.

Correlates of Consciousness

Are there some particular types of neurons, distributed over the visual neocortex, whose firing directly symbolizes the content of visual awareness? One very simplistic hypothesis is that the activities in the upper layers of the cortex are largely unconscious ones, whereas the activities in the lower layers (layers 5 and 6) mostly correlate with consciousness. We have wondered whether the pyramidal neurons in layer 5 of the neocortex, especially the larger ones, might play this latter role.

These are the only cortical neurons that project right out of the cortical system (that is, not to the neocortex, the thalamus or the claustrum). If visual awareness represents the results of neural computations in the cortex, one might expect that what the cortex sends elsewhere would symbolize those results. Moreover, the neurons in layer 5 show a rather unusual propensity to fire in bursts. The idea that layer 5 neurons may directly symbolize visual awareness is attractive, but it still is too early to tell whether there is anything in it.

Visual awareness is clearly a difficult problem. More work is needed on the psychological and neural basis of both attention and very short term memory. Studying the neurons when a percept changes, even though the visual input is constant, should be a powerful experimental paradigm. We need to construct neurobiological theories of visual awareness and test them using a combination of molecular, neurobiological and clinical imaging studies.

We believe that once we have mastered the secret of this simple form of awareness, we may be close to understanding a central mystery of human life: how the physical events occurring in our brains while we think and act in the world relate to our subjective sensations—that is, how the brain relates to the mind.

Postscript: There have been several relevant developments since this article was first published. It now seems likely that there are rapid "on-line" systems for stereotyped motor responses such as hand or eye movement. These systems are unconscious and lack memory. Conscious seeing, on the other hand, seems to be slower and more subject to visual illusions. The brain needs to form a conscious representation of the visual scene that it then can use for many different actions or thoughts. Exactly how all these pathways work and how they interact is far from clear.

There have been more experiments on the behavior of neurons that respond to bistable visual percepts, such as binocular rivalry, but it is probably too early to draw firm conclusions from them about the exact neural correlates of visual consciousness. We have suggested on theoretical grounds based on the the neuroanatomy of the macaque monkey that primates are not directly aware of what is happening in the primary visual cortex, even though most of the visual information flows through it. This hypothesis is supported by some experimental evidence, but it is still controversial. SA

Further Reading

PERCEPTION. Irvin Rock. Scientific American Library, 1984.

CONSCIOUSNESS AND THE COMPUTATIONAL MIND. Ray Jackendoff. MIT Press/Bradford Books, 1987.

COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, VOL. LV: THE BRAIN. Cold Spring Harbor Laboratory Press, 1990.

TOWARDS A NEUROBIOLOGICAL THEORY OF CONSCIOUSNESS. Francis Crick and Christof Koch in *Seminars in the Neurosciences,* Vol. 2, pages 263–275; 1990.

THE COMPUTATIONAL BRAIN. Patricia S. Churchland and Terrence J. Sejnowski. MIT Press/Bradford Books, 1992.

THE VISUAL BRAIN IN ACTION. A. David Milner and Melvyn A. Goodale. Oxford University Press, 1995.

ARE WE AWARE OF NEURAL ACTIVITY IN PRIMARY VISUAL CORTEX? Francis Crick and Christof Koch in *Nature,* Vol. 375, pages 121-123, May 11, 1995.

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The Puzzle of Conscious Experience

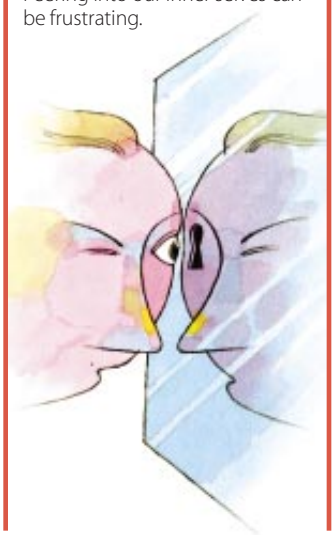
Neuroscientists and others are at last plumbing one of the most profound mysteries of existence. But knowledge of the brain alone may not get them to the bottom of it

by David J. Chalmers

The Author

DAVID J. CHALMERS studied mathematics at Adelaide University and as a Rhodes Scholar at the University of Oxford, but a fascination with consciousness led him into philosophy and cognitive science. He has a Ph.D. in these fields from Indiana University and is currently in the department of philosophy at the University of California, Santa Cruz. Chalmers has published numerous articles on artificial intelligence and the philosophy of mind.

Peering into our inner selves can be frustrating.



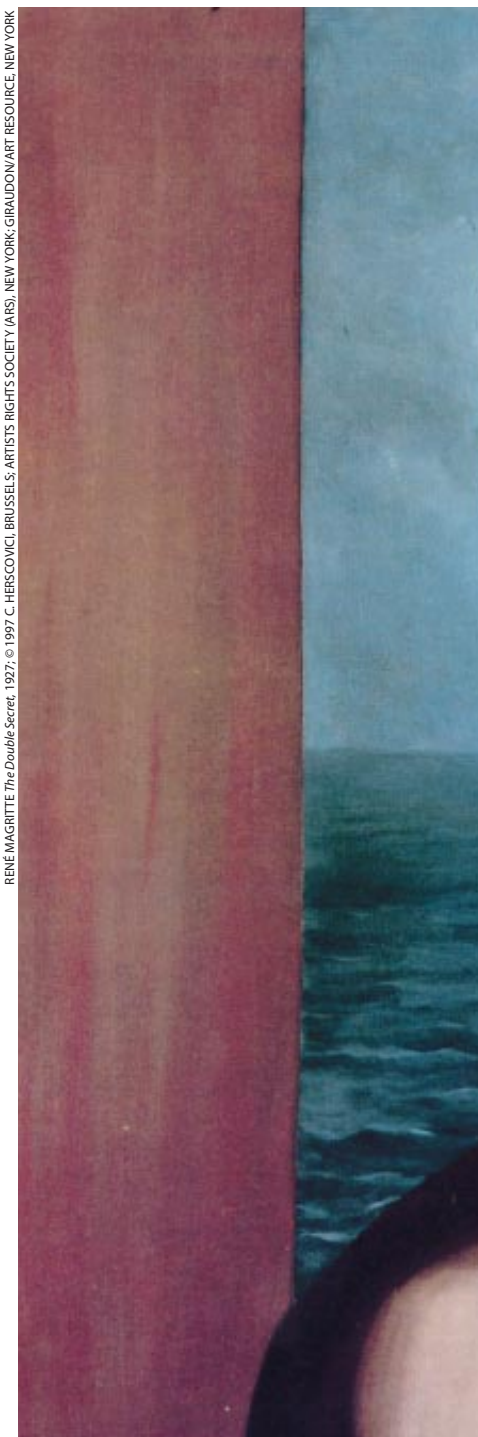
DUSAN PETRICIC

Conscious experience is at once the most familiar thing in the world and the most mysterious. There is nothing we know about more directly than consciousness, but it is extraordinarily hard to reconcile it with everything else we know. Why does it exist? What does it do? How could it possibly arise from neural processes in the brain? These questions are among the most intriguing in all of science.

From an objective viewpoint, the brain is relatively comprehensible. When you look at this page, there is a whir of processing: photons strike your retina, electrical signals are passed up your optic nerve and between different areas of your brain, and eventually you might respond with a smile, a perplexed frown or a remark. But there is also a subjective aspect. When you look at the page, you are conscious of it, directly experiencing the images and words as part of your private, mental life. You have vivid impressions of the colors and shapes of the images. At the same time, you may be feeling some emotions and forming some thoughts. Together such experiences make up consciousness: the subjective, inner life of the mind.

CONSCIOUSNESS, the subjective experience of an inner self, could be a phenomenon forever beyond the reach of neuroscience. Even a detailed knowledge of the brain's workings and the neural correlates of consciousness may fail to explain how or why human beings have self-aware minds.

For many years, consciousness was shunned by researchers studying the brain and the mind. The prevailing view was that science, which depends on objectivity, could not accommodate something as subjective as consciousness. The behaviorist movement in psychology, dominant earlier in this century, concentrated on external behavior and disallowed any talk of internal mental processes. Later, the rise of cognitive science focused attention on processes inside the head. Still, consciousness remained off-limits, fit only for late-night discussion over drinks.



RENÉ MAGRITTE *The Double Secret*, 1927; © 1997 C. HERSCOVICI, BRUSSELS; ARTISTS RIGHTS SOCIETY (ARS), NEW YORK; GIRAUDON/ART RESOURCE, NEW YORK

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Over the past several years, however, an increasing number of neuroscientists, psychologists and philosophers have been rejecting the idea that consciousness cannot be studied and are attempting to delve into its secrets. As might be expected of a field so new, there is a tangle of diverse and conflicting theories, often using basic concepts in incompatible ways. To help unsnarl the tangle, philosophical reasoning is vital.

The myriad views within the field range from reductionist theories, according to which consciousness can be explained by the standard methods of neuroscience and psychology, to the position of the so-called mysterians, who say we will never understand consciousness at all. I believe that on close analysis both of these views can be seen to be mistaken and that the truth lies somewhere in the middle.

Against reductionism I will argue that the tools of neuroscience cannot provide a full account of conscious experience, although they have much to offer. Against mysterianism I will hold that consciousness might be explained by a new kind of theory. The full details of such a theory are still out of reach, but careful reasoning and some educated inferences can reveal something of its general nature. For example, it will probably involve new fundamental laws, and the concept of information may play a central role. These faint glimmerings suggest that a theory of consciousness may have startling consequences for our view of the universe and of ourselves.

The Hard Problem

Researchers use the word "consciousness" in many different ways. To clarify the issues, we first have to separate the problems that are often clustered together under the name. For this

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purpose, I find it useful to distinguish between the "easy problems" and the "hard problem" of consciousness. The easy problems are by no means trivial—they are actually as challenging as most in psychology and biology—but it is with the hard problem that the central mystery lies.

The easy problems of consciousness include the following: How can a human subject discriminate sensory stimuli and react to them appropriately? How does the brain integrate information from many different sources and use this information to control behavior? How is it that subjects can verbalize their internal states? Although all these questions are associated with consciousness, they all concern the objective mechanisms of the cognitive system. Consequently, we have every reason to expect that continued work in cognitive psychology and neuroscience will answer them.

The hard problem, in contrast, is the question of how physical processes in the brain give rise to subjective experience. This puzzle involves the inner aspect of thought and perception: the way things feel for the subject. When we see, for example, we experience visual sensations, such as that of vivid blue. Or think of the ineffable sound of a distant oboe, the agony of an intense pain, the sparkle of happiness or the meditative quality of a moment lost in thought. All are part of what I call consciousness. It is these phenomena that pose the real mystery of the mind.

ISOLATED NEUROSCIENTIST in a black-and-white room knows everything about how the brain processes colors but does not know what it is like to see them. By itself, empirical knowledge of the brain does not yield complete knowledge of conscious experience.

To illustrate the distinction, consider a thought experiment devised by the Australian philosopher Frank Jackson. Suppose that Mary, a neuroscientist in the 23rd century, is the world's leading expert on the brain processes responsible for color vision. But Mary has lived her whole life in a black-and-white room and has never seen any other colors. She knows everything there is to know about physical processes in the brain—its biology, structure and function. This understanding enables her to grasp all there is to know about the easy problems: how the brain discriminates stimuli, integrates information and produces verbal reports. From her knowledge of color vision, she knows how color names correspond with wavelengths on the light spectrum. But there is still something crucial about color vision that Mary does not know:

Continued on page 34

BLACK-AND-WHITE PHOTOGRAPH BY DAN WAGNER; DIGITAL COMPOSITION BY TOM DRAPER DESIGN

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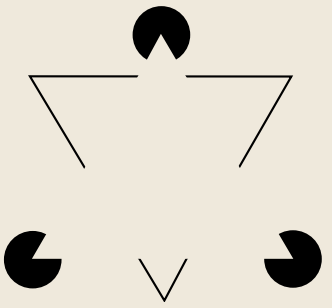
Why Neuroscience May Be Able to Explain Consciousness

by Francis Crick and Christof Koch

We believe that at the moment the best approach to the problem of explaining consciousness is to concentrate on finding what is known as the neural correlates of consciousness—the processes in the brain that are most directly responsible for consciousness. By locating the neurons in the cerebral cortex that correlate best with consciousness, and figuring out how they link to neurons elsewhere in the brain, we may come across key insights into what David J. Chalmers calls the hard problem: a full accounting of the manner in which subjective experience arises from these cerebral processes.

We commend Chalmers for boldly recognizing and focusing on the hard problem at this early stage, although we are not as enthusiastic about some of his thought experiments. As we see it, the hard problem can be broken down into several questions: Why do we experience anything at all? What leads to a particular conscious experience (such as the blueness of blue)? Why are some aspects of subjective experience impossible to convey to other people (in other words, why are they private)? We believe we have an answer to the last problem and a suggestion about the first two, revolving around a phenomenon known as explicit neuronal representation.



KANIZSA TRIANGLE stimulates neurons that code explicitly for such illusory contours.

What does "explicit" mean in this context? Perhaps the best way to define it is with an example. In response to the image of a face, say, ganglion cells fire all over the retina, much like the pixels on a television screen, to generate an implicit representation of the face. At the same time, they can also respond to a great many other features in the image, such as shadows, lines, uneven lighting and so on. In contrast, some neurons high in the hierarchy of the visual cortex respond mainly to the face or even to the face viewed at a particular angle. Such neurons help the brain represent the face in an explicit manner. Their loss, resulting from a stroke or some other brain injury, leads to prosopagnosia, an individual's inability to recognize familiar faces consciously—even his or her own, although the person can still identify a face as a face. Similarly, damage to other parts of the visual cortex can cause someone to lose the ability to experience color, while still seeing in shades of black and white, even though there is no defect in the color receptors in the eye.

At each stage, visual information is reencoded, typically in a semihierarchical manner. Retinal ganglion cells respond to a spot of light. Neurons in the primary visual cortex are most adept at responding to lines or edges; neurons higher up might prefer a moving contour. Still higher are those that respond to faces and other familiar objects. On top are those that project to pre-motor and motor structures in the brain, where they fire the neurons that initiate such actions as speaking or avoiding an oncoming automobile.

Chalmers believes, as we do, that the subjective aspects of an experience must relate closely to the firing of the neurons corresponding to those aspects (the neural correlates). He describes a well-known thought experiment, constructed around a hypothetical neuroscientist, Mary, who specializes in color perception but has never seen a color. We believe the reason Mary does not know what it is like to see a color, however, is that she has never had an explicit neural representation of a color in her brain, only of the words and ideas associated with colors.

In order to describe a subjective visual experience, the information has to be transmitted to the motor output stage of the brain, where it becomes available for verbalization or other actions. This transmission always involves reencoding the information, so that the explicit information expressed by the motor neurons is related, but not identical, to the explicit information expressed by the firing of the neurons associated with color experience, at some level in the visual hierarchy.

It is not possible, then, to convey with words and ideas the exact nature of a subjective experience. It is possible, however, to convey a difference between subjective experiences—to distinguish between red and orange, for example. This is possible because a difference in a high-level visual cortical area will still be associated with a difference in the motor stages. The implication is that we can never explain to other people the subjective nature of any conscious experience, only its relation to other ones.

The other two questions, concerning why we have conscious experiences and what leads to specific ones, appear more difficult. Chalmers proposes that they require the introduction of "experience" as a fundamental new feature of the world, relating to the ability of an organism to process information. But which types of neuronal information produce consciousness? And what makes a certain type of information correspond to the blueness of blue, rather than the greenness of green? Such problems seem as difficult as any in the study of consciousness.

We prefer an alternative approach, involving the concept of "meaning." In what sense can neurons that explicitly code for a face be said to convey the meaning of a face to the rest of the brain? Such a property must relate to the cells' projective field—the pattern of synaptic connections to neurons that code explicitly for related concepts. Ultimately, these connections extend to the motor output. For example, neurons responding to a certain face might be connected to ones expressing the name of the person whose face it is and to others for her voice, memories involving her and so on. Such associations among neurons must be behaviorally useful—in other words, consistent with feedback from the body and the external world.

Meaning derives from the linkages among these representations with others spread throughout the cortical system in a vast associational network, similar to a dictionary or a relational database. The more diverse these connections, the richer the meaning. If, as in our previous example of prosopagnosia, the synaptic output of such face neurons were blocked, the cells would still respond to the person's face, but there would be no associated meaning and, therefore, much less experience. Therefore, a face would be seen but not recognized as such.

Of course, groups of neurons can take on new functions, allowing brains to learn new categories (including faces) and associate new categories with existing ones. Certain primitive associations, such as pain, are to some extent inborn but subsequently refined in life.

Information may indeed be the key concept, as Chalmers suspects. Greater certainty will require consideration of highly parallel streams of information, linked—as are neurons—in complex networks. It would be useful to try to determine what features a neural network (or some other such computational embodiment) must have to generate meaning. It is possible that such exercises will suggest the neural basis of meaning. The hard problem of consciousness may then appear in an entirely new light. It might even disappear.

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Continued from page 32

what it is like to experience a color such as red. It follows that there are facts about conscious experience that cannot be deduced from physical facts about the functioning of the brain.

Indeed, nobody knows why these physical processes are accompanied by conscious experience at all. Why is it that when our brains process light of a certain wavelength, we have an experience of deep purple? Why do we have any experience at all? Could not an unconscious automaton have performed the same tasks just as well? These are questions that we would like a theory of consciousness to answer.

Is Neuroscience Enough?

I am not denying that consciousness arises from the brain. We know, for example, that the subjective experience of vision is closely linked to processes in the visual cortex. It is the link itself that perplexes, however. Remarkably, subjective experience seems to emerge from a physical process. But we have no idea how or why this is.

Given the flurry of recent work on consciousness in neuroscience and psychology, one might think this mystery is starting to be cleared up. On closer examination, however, it turns out that almost all the current work addresses only the easy problems of consciousness. The confidence of the reductionist view comes from the progress on the easy problems, but none of this makes any difference where the hard problem is concerned.

Consider the hypothesis put forward by neurobiologists Francis Crick of the Salk Institute for Biological Studies in San Diego and Christof Koch of the California Institute of Technology. They suggest that consciousness may arise from certain oscillations in the cerebral cortex, which become synchronized as neurons fire 40 times per second. Crick and Koch believe the phenomenon might explain how different attributes of a single perceived object (its color and shape, for example), which are processed in different parts of the brain, are merged into a coherent whole. In this theory, two pieces of information become bound together precisely when they are represented by synchronized neural firings.

The hypothesis could conceivably elucidate one of the easy problems about how information is integrated in the brain. But why should synchronized oscillations give rise to a visual experience, no matter how much integration is taking place? This question involves the hard problem, about which the theory has nothing to offer. Indeed, Crick and Koch are agnostic about whether the hard problem can be solved by science at all [*see box on preceding page*].

The same kind of critique could be applied to almost all the recent work on consciousness. In his 1991 book *Consciousness Explained,* philosopher Daniel C. Dennett laid out a sophisticated theory of how numerous independent processes in the brain combine to produce a coherent response to a perceived event. The theory might do much to explain how we produce verbal reports on our internal states, but it tells us very little about why there should be a subjective experience behind these reports. Like other reductionist theories, Dennett's is a theory of the easy problems.

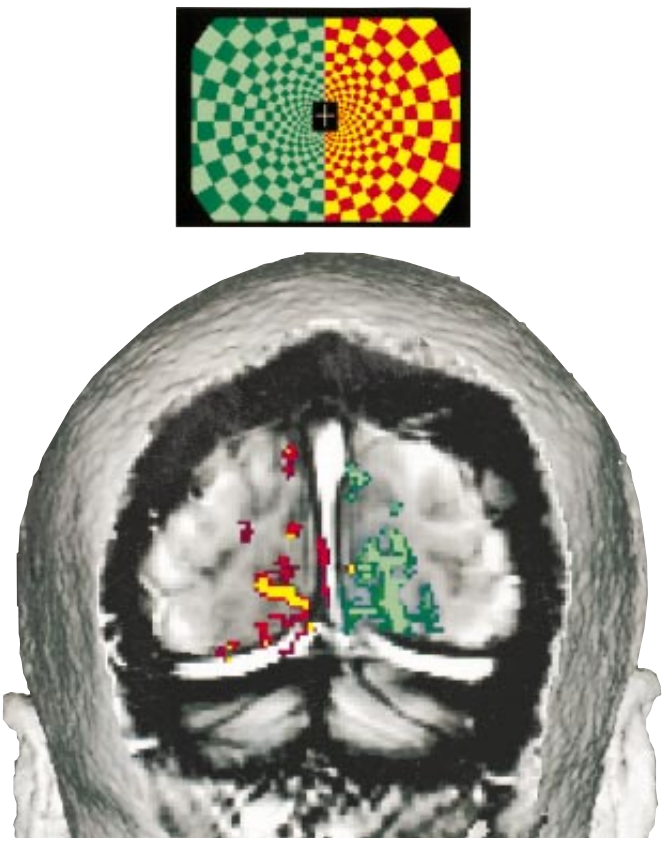
The critical common trait among these easy problems is that they all concern how a cognitive or behavioral function is performed. All are ultimately questions about how the brain carries out some task—how it discriminates stimuli, integrates information, produces reports and so on. Once neurobiology specifies appropriate neural mechanisms, showing how the functions are performed, the easy problems are solved.

The hard problem of consciousness, in contrast, goes beyond problems about how functions are performed. Even if every behavioral and cognitive function related to consciousness were explained, there would still remain a further mystery: Why is the performance of these functions accompanied by conscious experience? It is this additional conundrum that makes the hard problem hard.

The Explanatory Gap

Some have suggested that to solve the hard problem, we need to bring in new tools of physical explanation: nonlinear dynamics, say, or new discoveries in neuroscience, or quantum mechanics. But these ideas suffer from exactly the same difficulty. Consider a proposal from Stuart R. Hameroff of the University of Arizona and Roger Penrose of the University of Oxford. They hold that consciousness arises from quantum-physical processes taking place in microtubules, which are protein structures inside neurons. It is possible (if not likely) that such a hypothesis will lead to an explanation of how the brain makes decisions or even how it proves mathematical theorems, as Hameroff and Penrose suggest. But even if it does, the theory is silent about how these processes might give rise to conscious experience. Indeed, the same problem arises with any theory of consciousness based only on physical processing.

The trouble is that physical theories are best suited to



UNIVERSITY OF PITTSBURGH

BLOOD FLOW variations in the visual cortex demonstrate how a subject's brain responds to a pattern being viewed. The colors in this image show the cortical activity corre-

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explaining why systems have a certain physical structure and how they perform various functions. Most problems in science have this form; to explain life, for example, we need to describe how a physical system can reproduce, adapt and metabolize. But consciousness is a different sort of problem entirely, as it goes beyond the scientific explanation of structure and function.

Of course, neuroscience is not irrelevant to the study of consciousness. For one, it may be able to reveal the nature of the neural correlate of consciousness—the brain processes most directly associated with conscious experience. It may even give a detailed correspondence between specific processes in the brain and related components of experience. But until we know why these processes give rise to conscious experience at all, we will not have crossed what philosopher Joseph Levine has called the explanatory gap between physical processes and consciousness. Making that leap will demand a new kind of theory.

In searching for an alternative, a key observation is that not all entities in science are explained in terms of more basic entities. In physics, for example, space-time, mass and charge (among other things) are regarded as fundamental features of the world, as they are not reducible to anything simpler. Despite this irreducibility, detailed and useful theories relate these entities to one another in terms of fundamental laws. Together these features and laws explain a great variety of complex and subtle phenomena.

It is widely believed that physics provides a complete catalogue of the universe's fundamental features and laws. As physicist Steven Weinberg puts it in his 1992 book *Dreams of a Final Theory,* the goal of physics is a "theory of everything" from which all there is to know about the universe can be derived. But Weinberg concedes that there is a problem with consciousness. Despite the power of physical theory, the existence of consciousness does not seem to be derivable from physical laws. He defends physics by arguing that it might eventually explain what he calls the objective correlates of consciousness (that is, the neural correlates), but of course to do this is not to explain consciousness itself. If the existence of consciousness cannot be derived from physical laws, a theory of physics is not a true theory of everything. So a final theory must contain an additional fundamental component.

A True Theory of Everything

Toward this end, I propose that conscious experience be considered a fundamental feature, irreducible to anything more basic. The idea may seem strange at first, but consistency seems to demand it. In the 19th century it turned out that electromagnetic phenomena could not be explained in terms of previously known principles. As a consequence, scientists introduced electromagnetic charge as a new fundamental entity and studied the associated fundamental laws. Similar reasoning should be applied to consciousness. If existing fundamental theories cannot encompass it, then something new is required.

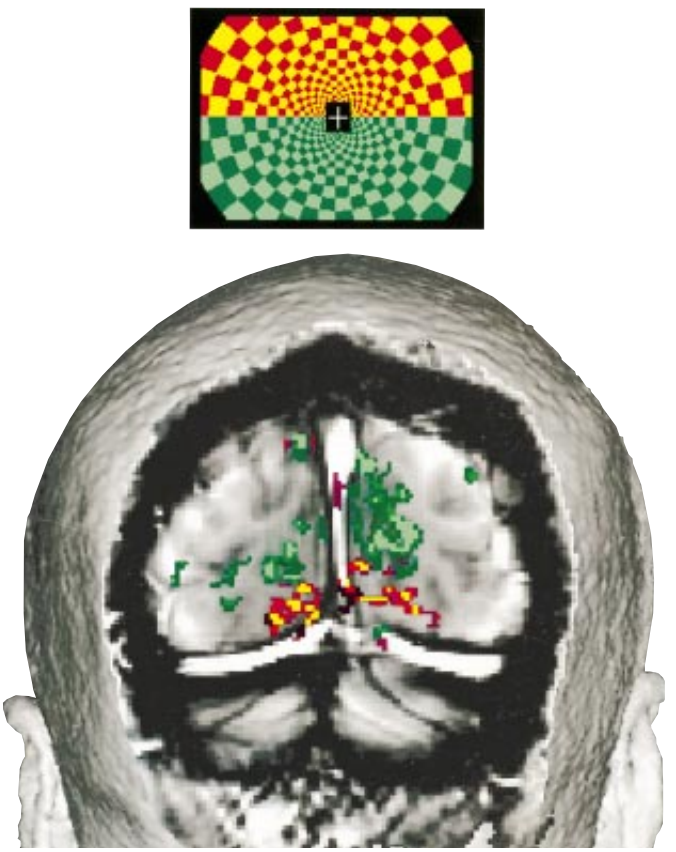
Where there is a fundamental property, there are fundamental laws. In this case, the laws must relate experience to elements of physical theory. These laws will almost certainly not interfere with those of the physical world; it seems that the latter form a closed system in their own right. Rather the laws will serve as a bridge, specifying how experience depends on underlying physical processes. It is this bridge that will cross the explanatory gap.

Thus, a complete theory will have two components: physical laws, telling us about the behavior of physical systems from the infinitesimal to the cosmological, and what we might call psychophysical laws, telling us how some of those systems are associated with conscious experience. These two components will constitute a true theory of everything.

Supposing for the moment that they exist, how might we uncover such psychophysical laws? The greatest hindrance in this pursuit will be a lack of data. As I have described it, consciousness is subjective, so there is no direct way to monitor it in others. But this difficulty is an obstacle, not a dead end. For a start, each one of us has access to our own experiences, a rich trove that can be used to formulate theories. We can also plausibly rely on indirect information, such as subjects' descriptions of their experiences. Philosophical arguments and thought experiments also have a role to play. Such methods have limitations, but they give us more than enough to get started.

These theories will not be conclusively testable, so they will inevitably be more speculative than those of more conventional scientific disciplines. Nevertheless, there is no reason they should not be strongly constrained to account accurately for our own first-person experiences, as well as the evidence from subjects' reports. If we find a theory that fits the data better than any other theory of equal simplicity, we will have good reason to accept it. Right now we do not have even a single theory that fits the data, so worries about testability are premature.

We might start by looking



sponding to the subject's view of either the vertical or horizontal half of the pattern. The experiment may illuminate a neural correlate of visual consciousness.

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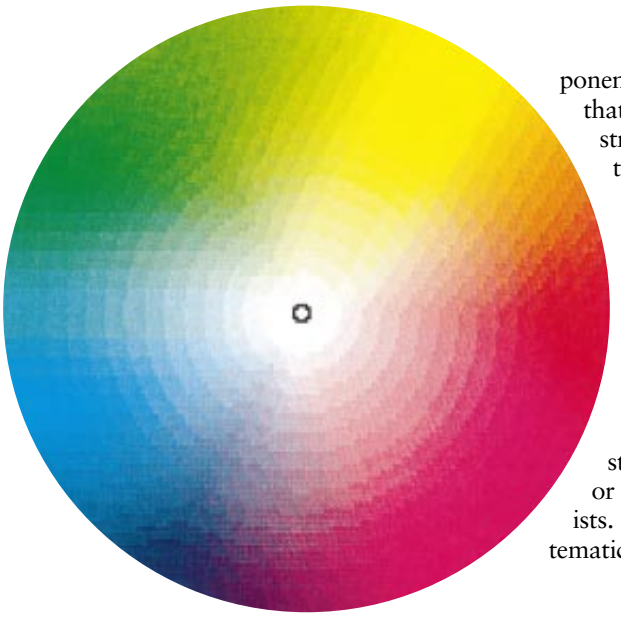

COLOR WHEEL arranges hues so that ones experienced as similar are closest. Nearby colors also correspond to similar perceptual representations in the brain.

for high-level bridging laws, connecting physical processes to experience at an everyday level. The basic contour of such a law might be gleaned from the observation that when we are conscious of something, we are generally able to act on it and speak about it—which are objective, physical functions. Conversely, when some information is directly available for action and speech, it is generally conscious. Thus, consciousness correlates well with what we might call "awareness": the process by which information in the brain is made globally available to motor processes such as speech and bodily action.

Objective Awareness

The notion may seem trivial. But as defined here, awareness is objective and physical, whereas consciousness is not. Some refinements to the definition of awareness are needed, in order to extend the concept to animals and infants, which cannot speak. But at least in familiar cases, it is possible to see the rough outlines of a psychophysical law: where there is awareness, there is consciousness, and vice versa.

To take this line of reasoning a step further, consider the structure present in the conscious experience. The experience of a field of vision, for example, is a constantly changing mosaic of colors, shapes and patterns and as such has a detailed geometric structure. The fact that we can describe this structure, reach out in the direction of many of its components and perform other actions that depend on it suggests that the structure corresponds directly to that of the information made available in the brain through the neural processes of objective awareness.

Similarly, our experiences of color have an intrinsic three-dimensional structure that is mirrored in the structure of information processes in the brain's visual cortex. This structure is illustrated in the color wheels and charts used by artists. Colors are arranged in a systematic pattern—red to green on one axis, blue to yellow on another, and black to white on a third. Colors that are close to one another on a color wheel are experienced as similar [*see illustration on this page*]. It is extremely likely that they also correspond to similar perceptual representations in the brain, as part of a system of complex three-dimensional coding among neurons that is not yet fully understood. We can recast the underlying concept as a principle of structural coherence: the structure of conscious experience is mirrored by the structure of information in awareness, and vice versa.

Another candidate for a psychophysical law is a principle of organizational invariance. It holds that physical systems with the same abstract organization will give rise to the same kind of conscious experience, no matter what they are made of. For example, if the precise interactions between our neurons could be duplicated with silicon chips, the same conscious experience would arise. The idea is somewhat controversial, but I believe it is strongly supported by thought experiments describing the gradual replacement of neurons by silicon chips [*see box on next page*]. The remarkable implication is that consciousness might someday be achieved in machines.

The ultimate goal of a theory of consciousness is a simple and elegant set of fundamental laws, analogous to the fundamental laws of physics. The principles described above are unlikely to be fundamental, however. Rather they seem to be high-level psychophysical laws, analogous to macroscopic principles in physics such as those of thermodynamics or kinematics. What might the underlying fundamental laws be? No one knows, but I don't mind speculating.

I suggest that the primary psychophysical laws may centrally involve the concept of information. The abstract notion of information, as put forward in the 1940s by Claude E. Shannon of the Massachusetts Institute of Technology, is that of a set of separate states with a basic structure of similarities and differences between them. We can think of a 10-bit binary code as an information state, for example. Such information states can be embodied in the physical world. This happens whenever they correspond to physical states (voltages, say), and when differences between them can be transmitted along some pathway, such as a telephone line.

Information: Physical and Experiential

We can also find information embodied in conscious experience. The pattern of color patches in a visual field, for example, can be seen as analogous to that of the pixels covering a display screen. Intriguingly, it turns out that we find the same information states embedded in conscious experience and in underlying physical processes in the brain. The three-dimensional encoding of color spaces, for example, suggests that the information state in a color experience corresponds directly to an information state in the brain. Thus, we might even regard the two states as distinct aspects of a single information state, which is simultaneously embodied in both physical processing and conscious experience.

A natural hypothesis ensues. Perhaps information, or at least some information, has two basic aspects: a physical one and an experiential one. This hypothesis has the status of a fundamental principle that might underlie the relation between physical processes and experience. Wherever we find conscious experience, it exists as one aspect of an information state, the other aspect of which is embedded in a physical process in the brain. This proposal needs to be fleshed out to make a satisfying theory. But it fits nicely with the principles mentioned earlier—systems with the same organization will embody the same information, for example—and it could explain numerous features of our conscious experience.

The idea is at least compatible with several others, such as physicist John A.

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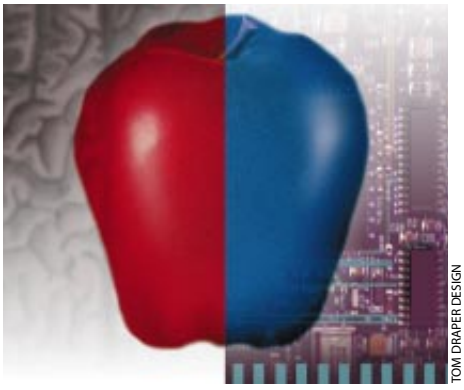
Dancing Qualia in a Synthetic Brain

Whether consciousness could arise in a complex, synthetic system is a question many people find intrinsically fascinating. Although it may be decades or even centuries before such a system is built, a simple thought experiment offers strong evidence that an artificial brain, if organized appropriately, would indeed have precisely the same kind of conscious experiences as a human being.

Consider a silicon-based system in which the chips are organized and function in the same way as the neurons in your brain. That is, each chip in the silicon system does exactly what its natural analogue does and is interconnected to surrounding elements in precisely the same way. Thus, the behavior exhibited by the artificial system will be exactly the same as yours. The crucial question is: Will it be conscious in the same way that you are?

Let us assume, for the purpose of argument, that it would not be. (Here we use a reasoning technique known as reductio ad absurdum, in which the opposite hypothesis is assumed and then shown to lead to an untenable conclusion.) That is, it has either different experiences—an experience of blue, say, when you are seeing red—or no experience at all. We will consider the first case; the reasoning proceeds similarly in both cases.



TOM DRAPER DESIGN

IN THOUGHT EXPERIMENT, an apple might flash from red to blue.

Because chips and neurons have the same function, they are interchangeable, with the proper interfacing. Chips therefore can replace neurons, producing a continuum of cases in which a successively larger proportion of neurons are replaced by chips. Along this continuum, the conscious experience of the system will also change. For example, we might replace all the neurons in your visual cortex with an identically organized version made of silicon. The resulting brain, with an artificial visual cortex, will have a different conscious experience from the original: where you had previously seen red, you may now experience purple (or perhaps a faded pink, in the case where the wholly silicon system has no experience at all).

Both visual cortices are then attached to your brain, through a two-position switch. With the switch in one mode, you use the natural visual cortex; in the other, the artificial cortex is activated. When the switch is flipped, your experience changes from red to purple, or vice versa. When the switch is flipped repeatedly, your experiences "dance" between the two different conscious states (red and purple), known as qualia.

Because your brain's organization has not changed, however, there can be no behavioral change when the switch is thrown. Therefore, when asked about what you are seeing, you will say that nothing has changed. You will hold that you are seeing red and have seen nothing but red—even though the two colors are dancing before your eyes. This conclusion is so unreasonable that it is best taken as a reductio ad absurdum of the original assumption—that an artificial system with identical organization and functioning has a different conscious experience from that of a neural brain. Retraction of the assumption establishes the opposite: that systems with the same organization have the same conscious experience. —*D.J.C.*

Wheeler's suggestion that information is fundamental to the physics of the universe. The laws of physics might ultimately be cast in informational terms, in which case we would have a satisfying congruence between the constructs in both physical and psychophysical laws. It may even be that a theory of physics and a theory of consciousness could eventually be consolidated into a single grander theory of information.

Is Experience Ubiquitous?

A potential problem is posed by the ubiquity of information. Even a thermostat embodies some information, for example, but is it conscious? There are at least two possible responses. First, we could constrain the fundamental laws so that only some information has an experiential aspect, perhaps depending on how it is physically processed. Second, we might bite the bullet and allow that all information has an experiential aspect—where there is complex information processing, there is complex experience, and where there is simple information processing, there is simple experience. If this is so, then even a thermostat might have experiences, although they would be much simpler than even a basic color experience, and there would certainly be no accompanying emotions or thoughts. This seems odd at first, but if experience is truly fundamental, we might expect it to be widespread. In any case, the choice between these alternatives should depend on which can be integrated into the most powerful theory.

Of course, such ideas may be all wrong. On the other hand, they might evolve into a more powerful proposal that predicts the precise structure of our conscious experience from physical processes in our brains. If this project succeeds, we will have good reason to accept the theory. If it fails, other avenues will be pursued, and alternative fundamental theories may be developed. In this way, we may one day resolve the greatest mystery of the mind. SA

Further Reading

ABSENT QUALIA, FADING QUALIA, DANCING QUALIA. David J. Chalmers in *Conscious Experience*. Edited by Thomas Metzinger. Ferdinand Schöningh, 1995.

EXPLAINING CONSCIOUSNESS: THE "HARD PROBLEM." Special issue of *Journal of Consciousness Studies*, Vol. 2, No. 3; Autumn 1995.

THE CONSCIOUS MIND: IN SEARCH OF A FUNDAMENTAL THEORY. David J. Chalmers. Oxford University Press, 1996.

THE NATURE OF CONSCIOUSNESS: PHILOSOPHICAL DEBATES. Edited by Ned Block, Owen Flanagan and Güven Güzeldere. MIT Press (in press).

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The Pursuit of Happiness

New research uncovers some anti-intuitive insights into how many people are happy—and why

by David G. Myers and Ed Diener

The Authors

DAVID G. MYERS and ED DIENER have been studying happiness for more than 10 years. Myers is professor of psychology at Hope College in Michigan and author of *The Pursuit of Happiness: Who Is Happy and Why* (William Morrow, 1992). He won the Gordon Allport Prize for his studies of group influence. Diener is professor of psychology at the University of Illinois and investigates the definition and measurement of subjective well-being. His current work focuses on cultural differences in subjective well-being and on adaptation to life events.

Wealth, it turns out, is not a good predictor of happiness.

DIMITRY SCHIDLOVSKY

Compared with misery, happiness is relatively unexplored terrain for social scientists. Between 1967 and 1994, 46,380 articles indexed in *Psychological Abstracts* mentioned depression, 36,851 anxiety, and 5,099 anger. Only 2,389 articles spoke of happiness, 2,340 life satisfaction, and 405 joy.

Recently we and other researchers have begun a systematic study of happiness. During the past two decades, dozens of investigators throughout the world have asked several hundred thousand representatively sampled people to reflect on their happiness and satisfaction with life—or what psychologists call "subjective well-being." In the U.S. the National Opinion Research Center at the University of Chicago has surveyed a representative sample of roughly 1,500 people a year since 1957; the Institute for Social Research at the University of Michigan has carried out similar studies on a less regular basis, as has the Gallup Organization. Government-funded efforts have also probed the moods of European citizens.

We have uncovered some surprising findings. People are happier than one might expect, and happiness does not appear to depend significantly on external circumstances. Although viewing life as a tragedy has a long and honorable history, the responses of random samples of people around the world about their happiness paints a much rosier picture.

In the University of Chicago surveys, three in 10 Americans say they are very happy, for example. Only one in 10 chooses the most negative description, "not too happy." The majority describe themselves as "pretty happy." (The few exceptions to global reports of reasonable happiness include hospitalized alcoholics, new inmates, new psychotherapy clients, South African blacks during apartheid, and students living under conditions of economic and political oppression.)

How can social scientists measure something as hard to pin down as happiness? Most researchers simply ask people to report their feelings of happiness or unhappiness and to assess how satisfying their lives are. Such self-reported well-being is moderately consistent over years of retesting. Furthermore, those who say they are happy and satisfied seem happy to their close friends and family members and to a psychologist-interviewer. Their daily mood ratings reveal more positive emotions, and they smile more than those who call themselves unhappy. Self-reported happiness also predicts other indicators of well-being. Compared with the depressed, happy people are less self-focused, less hostile and abusive, and less susceptible to disease.

People who say they are happy and satisfied seem happy to their family and friends. Happy people also are less susceptible to disease.

We have found that the even distribution of happiness cuts across almost all demographic classifications of age, economic class, race and educational level. In addition, almost all research strategies for assessing subjective well-being—including those that sample people's experience by polling them at random times with beepers—turn up similar findings.

Interviews with representative samples of people of all ages, for example, reveal that no time of life is notably happier or unhappier. Similarly, men and women are equally likely to declare themselves "very happy" and "satisfied" with life, according to a statistical digest of 146 studies by Marilyn J. Haring, William Stock and Morris A. Okun, all then at Arizona State University. Alex Michalos of the University of Northern

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Probing for Happiness

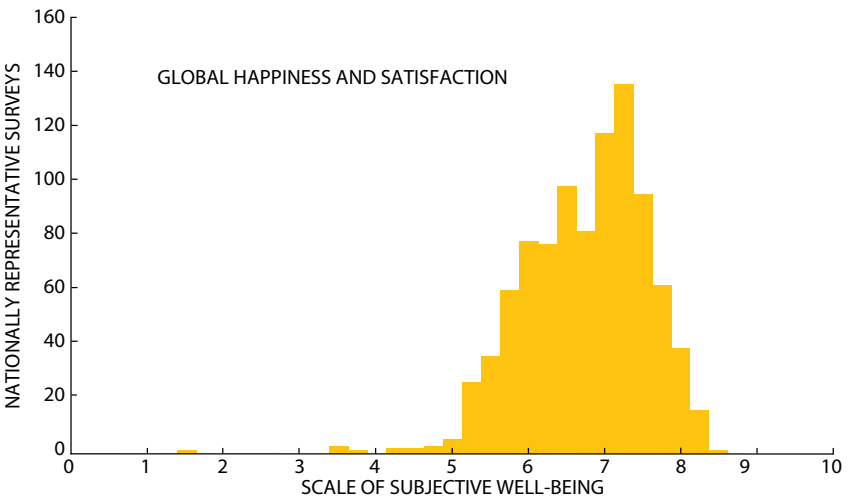
Researchers use various methods to survey people's subjective sense of well-being. Some employ images (*top*), others use words (*middle*), but all questions essentially come down to asking people how they feel about their life. Different techniques yield remarkably similar results; we have collated data from almost 1,000 surveys of 1.1 million people to arrive at a global estimate of reported subjective well-being (*bottom*). *—D.G.M. and E.D.*

WHICH OF THESE FACES REPRESENTS
THE WAY YOU FEEL ABOUT YOUR LIFE AS A WHOLE?

20% 46% 27% 4% 2% 1% 0%

"In most ways my life is close to my ideal."
"The conditions of my life are excellent."
"I am satisfied with my life."
"So far I have gotten the important things I want in life."
"If I could live my life over, I would change almost nothing."

Do you strongly disagree, disagree, slightly disagree, neither agree nor disagree, slightly agree, agree or strongly agree?



DIMITRY SCHIDLOVSKY

British Columbia and Ronald Inglehart of the University of Michigan, summarizing newer surveys of 18,000 university students in 39 countries and 170,000 adults in 16 countries, corroborate these findings.

Knowing someone's ethnicity also gives little clue to subjective well-being. African-Americans are only slightly less likely than European-Americans to feel very happy. The National Institute of Mental Health found that rates of depression and alcoholism among blacks and whites are roughly equal. Social psychologists Jennifer K. Crocker of the University of Michigan and Brenda Major of the University of California at Santa Barbara assert that people in disadvantaged groups maintain self-esteem by valuing things at which they excel, by making comparisons within their own groups and by blaming problems on external sources such as prejudice.

What Money Can't Buy

Wealth is also a poor predictor of happiness. People have not become happier over time as their cultures have become more affluent. Even though Americans earn twice as much in today's dollars as they did in 1957, the proportion of those telling surveyors from the National Opinion Research Center that they are "very happy" has declined from 35 to 29 percent.

Even very rich people—those surveyed among *Forbes* magazine's 100 wealthiest Americans—are only slightly happier than the average American. Those whose income has increased over a 10-year period are not happier than those whose income is stagnant. Indeed, in most nations the correlation between income and happiness is negligible—only in the poorest countries, such as Bangladesh and India, is income a good measure of emotional well-being.

Are people in rich countries happier, by and large, than people in not so rich countries? It appears in general that they are, but the margin may be slim. In Portugal, for example, only one in 10 people reports being very happy, whereas in the much more prosperous Netherlands the proportion of very happy people is four in 10. Yet there are curious reversals in this correlation between national wealth and well-being—the Irish during the 1980s consistently reported greater life satisfaction than the wealthier West Germans. Furthermore, other factors, such as civil rights, literacy and duration

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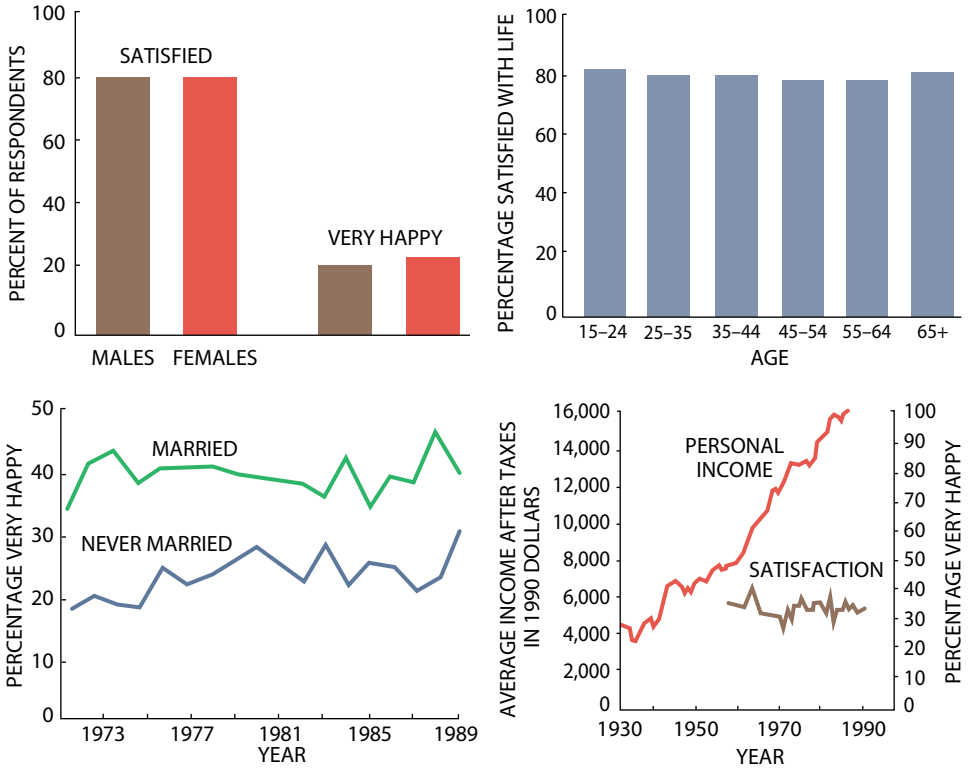

DIMITRY SCHIDLOVSKY

SOURCE: Top graphs: *Based on data reported by Ronald Inglehart in* Culture Shift in Advanced Industrial Society, *Princeton University Press, 1989*

SOURCE: Bottom graphs: *National Opinion Research Center, University of Chicago*

HAPPINESS APPEARS CONSISTENT across many different sectors of the population. Both sexes report roughly the same satisfaction with life (*top left*), as do various age groups (*top right*). Among the few consistent differentials is that between married and never-married people (*bottom left*); other data indicate that divorced people are less happy than either of these two groups. Personal satisfaction has remained relatively constant over at least several decades in the U.S., even as national income has increased (*bottom right*).

of democratic government, all of which also promote reported life satisfaction, tend to go hand in hand with national wealth. As a result, it is impossible to tell whether the happiness of people in wealthier nations is based on money or is a by-product of other felicities.

Habits of Happy People

Although happiness is not easy to predict from material circumstances, it seems consistent for those who have it. In one National Institute on Aging study of 5,000 adults, the happiest people in 1973 were still relatively happy a decade later, despite changes in work, residence and family status.

In study after study, four traits characterize happy people. First, especially in individualistic Western cultures, they like themselves. They have high self-esteem and usually believe themselves to be more ethical, more intelligent, less prejudiced, better able to get along with others, and healthier than the average person. (Such findings bring to mind Sigmund Freud's joke about the man who told his wife, "If one of us should die, I think I would go live in Paris.")

Second, happy people typically feel personal control. Those with little or no control over their lives—such as prisoners, nursing home patients, severely impoverished groups or individuals, and citizens of totalitarian regimes—suffer lower morale and worse health. Third, happy people are usually optimistic. Fourth, most happy people are extroverted. Although one might expect that introverts would live more happily in the serenity of their less stressed, contemplative lives, extroverts are happier—whether alone or with others.

The causal arrows for these correlations are uncertain. Does happiness make people more outgoing, or are outgoing people more likely to be happy, perhaps explaining why they marry sooner, get better jobs and make more friends? If extrovert traits do indeed predispose their carriers to happiness, people might become happier by acting in certain ways. In experiments, people who feign high self-esteem report feeling more positively about themselves, for example.

Whatever the reason, the close personal relationships that characterize happy lives are also correlated with health. Compared with loners, those who can name several intimate friends are healthier and less likely to die prematurely. For more than nine out of 10 people, the most significant alternative to aloneness is marriage. Although broken marital relationships can cause much misery, a good marriage apparently is a strong source of support. During the 1970s and 1980s, 39 percent of married adults told the National Opinion Research Center they were "very happy," as compared with 24 percent of those who had never married. In other surveys, only 12 percent of those who had divorced perceived themselves to be "very happy." The happiness gap between the married and the never married was similar for women and men.

Religiously active people also report greater happiness. One Gallup survey found that highly religious people were twice as likely as those lowest in spiritual commitment to declare themselves very happy. Other surveys, including a collaborative study of 166,000 people in 16 nations, have found that reported happiness and life satisfaction rise with strength of religious affiliation and frequency of attendance at worship services. Some researchers believe that religious affiliation entails greater social support and hopefulness.

Students of happiness are now beginning to examine happy people's exercise patterns, worldviews and goals. It is possible that some of the patterns discovered in the research may offer clues for transforming circumstances and behaviors that work against well-being into ones that promote it. Ultimately, then, the scientific study of happiness could help us understand how to build a world that enhances human well-being and to aid people in getting the most satisfaction from their circumstances. SA

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Manic-Depressive Illness and Creativity

Does some fine madness plague great artists? Several studies now show that creativity and mood disorders are linked

by Kay Redfield Jamison

The Author

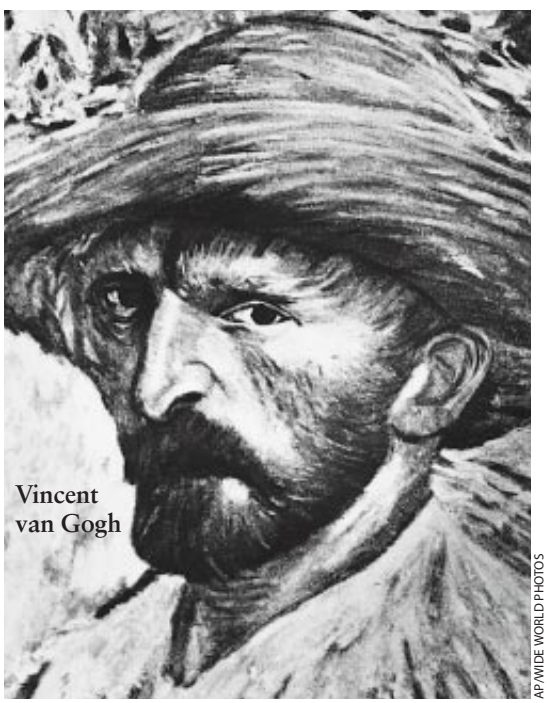
KAY REDFIELD JAMISON is professor of psychiatry at the Johns Hopkins University School of Medicine. She wrote *Touched with Fire: Manic-Depressive Illness and the Artistic Temperament* and co-authored the medical text *Manic-Depressive Illness*. Jamison is a member of the National Advisory Council for Human Genome Research and clinical director of the Dana Consortium on the Genetic Basis of Manic-Depressive Illness. She has also written and produced a series of public television specials about manic-depressive illness and the arts.

Van Gogh painted flowers while in the asylum at Saint-Rémy.

"Men have called me mad," wrote Edgar Allan Poe, "but the question is not yet settled, whether madness is or is not the loftiest intelligence—whether much that is glorious—whether all that is profound—does not spring from disease of thought—from moods of mind exalted at the expense of the general intellect."

Many people have long shared Poe's suspicion that genius and insanity are entwined. Indeed, history holds countless examples of "that fine madness." Scores of influential 18th- and 19th-century poets, notably William Blake, Lord Byron and Alfred, Lord Tennyson, wrote about the extreme mood swings they endured. Modern American poets John Berryman, Randall Jarrell, Robert Lowell, Sylvia Plath, Theodore Roethke, Delmore Schwartz and Anne Sexton were all hospitalized for either mania or depression during their lives. And many painters and composers, among them Vincent van Gogh, Georgia O'Keeffe, Charles Mingus and Robert Schumann, have been similarly afflicted.

Judging by current diagnostic criteria, it seems that most of these artists—and many others besides—suffered from one of the major mood disorders, namely, manic-depressive illness or major depression. Both are fairly common, very treatable and yet frequently lethal diseases. Major depression induces intense melancholic spells, whereas manic-depression,



Vincent van Gogh

AP/WIDE WORLD PHOTOS

Tennessee Williams

Reprinted from the February 1995 issue

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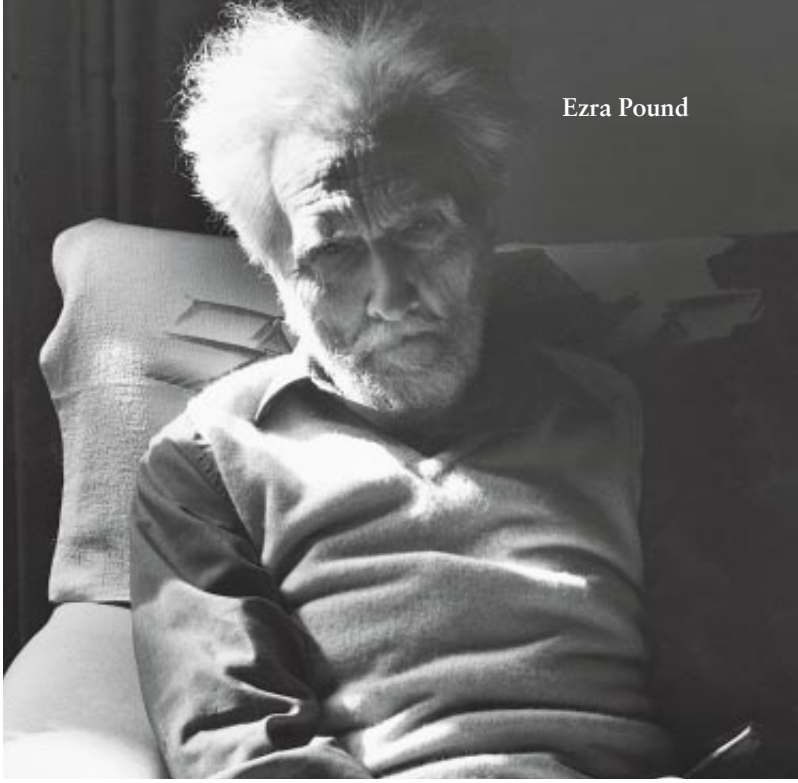
UPI/BETTMANN

Anne Sexton



HENRI CARTIER-BRESSON *Magnum*

Ezra Pound

a strongly genetic disease, pitches patients repeatedly from depressed to hyperactive and euphoric, or intensely irritable, states. In its milder form, termed cyclothymia, manic-depression causes pronounced but not totally debilitating changes in mood, behavior, sleep, thought patterns and energy levels. Advanced cases are marked by dramatic, cyclic shifts.

Could such disruptive diseases convey certain creative advantages? Many people find that proposition counterintuitive. Most manic-depressives do not possess extraordinary imagination, and most accomplished artists do not suffer from recurring mood swings. To assume, then, that such diseases usually promote artistic talent wrongly reinforces simplistic notions of the "mad genius." Worse yet, such a generalization trivializes a very serious medical condition and, to some degree, discredits individuality in the arts as well. It would be wrong to label anyone who is unusually accomplished, energetic, intense, moody or eccentric as manic-depressive. All the same, recent studies indicate that a high number of established artists—far more than could be expected by chance—meet the diagnostic criteria for manic-depression or major depression given in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*). In fact, it seems that these diseases can sometimes enhance or otherwise contribute to creativity in some people.

By virtue of their prevalence alone, it is clear that mood disorders do not necessarily breed genius. Indeed, 1 percent of the general population suffer from manic-depression, also called bipolar disorder, and 5 percent from a major depression, or unipolar disorder, during their lifetime. Depression affects twice as many women as men and most often, but not always, strikes later in life. Bipolar disorder afflicts equal numbers of women and men, and more than a third of all cases surface before age 20. Some 60 to 80 percent of all adoles-

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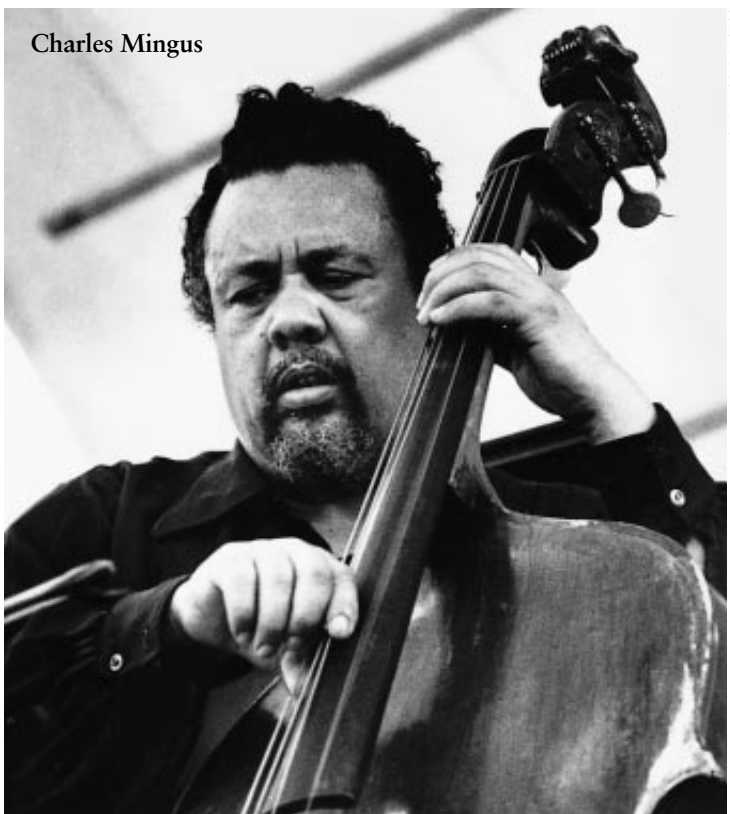

Charles Mingus

AP/WIDE WORLD PHOTOS

ARTISTS, writers and composers shown on these pages all most likely suffered from manic-depressive illness or major depressive illness, according to their letters and journals, medical records and accounts by their families and friends. Recent studies indicate that the temperaments and cognitive styles associated with mood disorders can in fact enhance creativity in some individuals.

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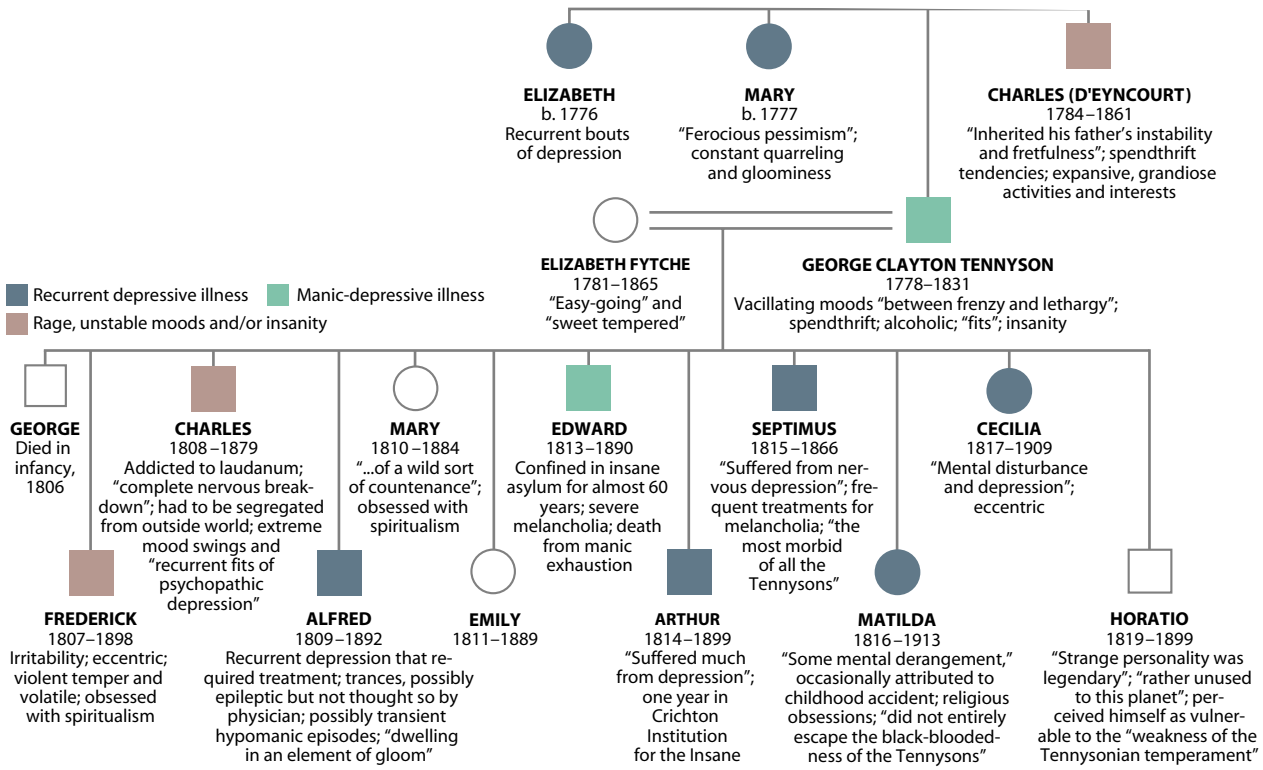
The Tainted Blood of the Tennysons

Alfred, Lord Tennyson (*right*), who experienced recurrent, debilitating depressions and probable hypomanic spells, often expressed fear that he might inherit the madness, or "taint of blood," in his family. His father, grandfather, two of his great-grandfathers as well as five of his seven brothers suffered from insanity, melancholia, uncontrollable rage or what is today known as manic-depressive illness. His brother Edward was confined to an asylum for nearly 60 years before he died from manic exhaustion. Lionel Tennyson, one of Alfred's two sons, displayed a mercurial temperament, as did one of his three grandsons.

CORBIS-BETTMANN

Modern medicine has confirmed that manic-depression and creativity tend to run in certain families. Studies of twins provide strong evidence for the heritability of manic-depressive illness. If an identical twin has manic-depressive illness, the other twin typically has a 70 to 100 percent chance of also having the disease; if the other twin is fraternal, the chances are considerably lower (approximately 20 percent). A review of pairs of identical twins reared apart from birth—in which at least one had been diagnosed as manic-depressive—found that in two thirds or more of the sets, the illness was present in both twins. *—K. R. J.*


ELIZABETH
b. 1776
Recurrent bouts of depression
MARY
b. 1777
"Ferocious pessimism"; constant quarreling and gloominess
CHARLES (D'EYNCOURT)
1784–1861
"Inherited his father's instability and fretfulness"; spendthrift tendencies; expansive, grandiose activities and interests
ELIZABETH FYTCHE
1781–1865
"Easy-going" and "sweet tempered"
GEORGE CLAYTON TENNYSON
1778–1831
Vacillating moods "between frenzy and lethargy"; spendthrift; alcoholic; "fits"; insanity
Recurrent depressive illness
Manic-depressive illness
Rage, unstable moods and/or insanity
GEORGE
Died in infancy, 1806
CHARLES
1808–1879
Addicted to laudanum; "complete nervous breakdown"; had to be segregated from outside world; extreme mood swings and "recurrent fits of psychopathic depression"
MARY
1810–1884
"...of a wild sort of countenance"; obsessed with spiritualism
EDWARD
1813–1890
Confined in insane asylum for almost 60 years; severe melancholia; death from manic exhaustion
SEPTIMUS
1815–1866
"Suffered from nervous depression"; frequent treatments for melancholia; "the most morbid of all the Tennysons"
CECILIA
1817–1909
"Mental disturbance and depression"; eccentric
FREDERICK
1807–1898
Irritability; eccentric; violent temper and volatile; obsessed with spiritualism
ALFRED
1809–1892
Recurrent depression that required treatment; trances, possibly epileptic but not thought so by physician; possibly transient hypomanic episodes; "dwelling in an element of gloom"
EMILY
1811–1889
ARTHUR
1814–1899
"Suffered much from depression"; one year in Crichton Institution for the Insane
MATILDA
1816–1913
"Some mental derangement," occasionally attributed to childhood accident; religious obsessions; "did not entirely escape the black-blooded-ness of the Tennysons"
HORATIO
1819–1899
"Strange personality was legendary"; "rather unused to this planet"; perceived himself as vulnerable to the "weakness of the Tennysonian temperament"

SOURCE: Adapted from Touched with Fire: Manic-Depressive Illness and the Artistic Temperament; *based on biographies, autobiographical writings and letters.*

LISA BURNETT

cents and adults who commit suicide have a history of bipolar or unipolar illness. Before the late 1970s, when the drug lithium first became widely available, one person in five with manic-depression committed suicide.

Major depression in both unipolar and bipolar disorders manifests itself through apathy, lethargy, hopelessness, sleep disturbances, slowed physical movements and thinking, impaired memory and concentration, and a loss of pleasure in typically enjoyable events. The diagnostic criteria also include suicidal thinking, self-blame and inappropriate guilt. To distinguish clinical depression from normal periods of unhappiness, the common guidelines further require that these symptoms persist for a minimum of two to four weeks and also that they significantly interfere with a person's everyday functioning.

Mood Elevation

During episodes of mania or hypomania (mild mania), bipolar patients experience symptoms that are in many ways the opposite of those associated with depression. Their mood and self-esteem are elevated. They sleep less and have abundant energy; their productivity increases. Manics frequently become paranoid and irritable. Moreover, their speech is often rapid, excitable and intrusive, and their thoughts move quickly and fluidly from one topic to another. They usually hold tremendous conviction about the correctness and importance of their own ideas as well. This grandiosity can contribute to poor judgment and impulsive behavior.

Hypomanics and manics generally have chaotic personal and professional relationships. They may spend large sums of money, drive recklessly or pursue questionable business ventures or sexual liaisons. In some cases, manics

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suffer from violent agitation and delusional thoughts as well as visual and auditory hallucinations.

Rates of Mood Disorders

For years, scientists have documented some kind of connection between mania, depression and creative output. In the late 19th and early 20th centuries, researchers turned to accounts of mood disorders written by prominent artists, their physicians and friends. Although largely anecdotal, this work strongly suggested that renowned writers, artists and composers—and their first-degree relatives—were far more likely to experience mood disorders and to commit suicide than was the general population. During the past 20 years, more systematic studies of artistic populations have confirmed these findings [*see illustration below*]. Diagnostic and psychological analyses of living writers and artists can give quite meaningful estimates of the rates and types of psychopathology they experience.

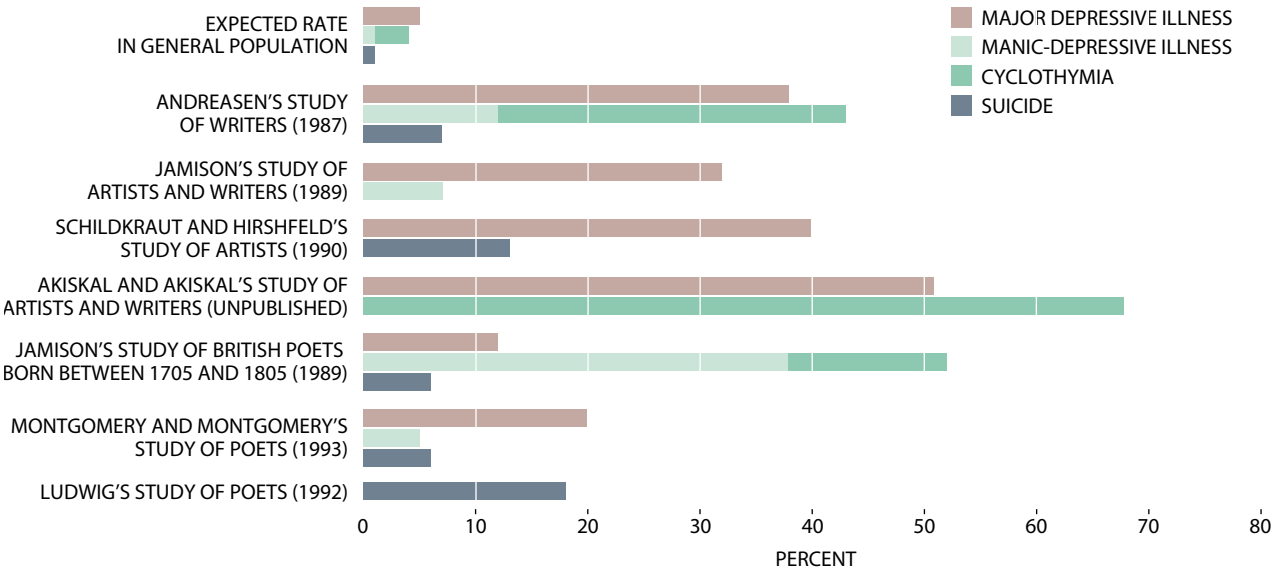
In the 1970s Nancy C. Andreasen of the University of Iowa completed the first of these rigorous studies, which made use of structured interviews, matched control groups and strict diagnostic criteria. She examined 30 creative writers and found an extraordinarily high occurrence of mood disorders and alcoholism among them. Eighty percent had experienced at least one episode of major depression, hypomania or mania; 43 percent reported a history of hypomania or mania. Also, the relatives of these writers, compared with the relatives of the control subjects, generally performed more creative work and more often had a mood disorder.

A few years later, while on sabbatical in England from the University of California at Los Angeles, I began a study of 47 distinguished British writers and visual artists. To select the group as best I could for creativity, I purposefully chose painters and sculptors who were Royal Academicians or Associates of the Royal Academy. All the playwrights had won the New York Drama Critics Award or the Evening Standard Drama (London Critics) Award, or both. Half of the poets were already represented in the *Oxford Book of Twentieth Century English Verse*. I found that 38 percent of these artists and writers had in fact been previously treated for a mood disorder; three fourths of those treated had required medication or hospitalization, or both. And half of the poets—the largest fraction from any one group—had needed such extensive care.

Hagop S. Akiskal of the University of California at San Diego, also affiliated with the University of Tennessee at Memphis, and his wife, Kareen Akiskal, subsequently interviewed 20 award-winning European writers, poets, painters and sculptors. Some two thirds of their subjects exhibited recurrent cyclothymic or hypomanic tendencies, and half had at one time suffered from a major depression. In collaboration with David H. Evans of the University of Memphis, the Akiskals noted the same trends among living blues musicians. More recently Stuart A. Montgomery and his wife, Deirdre B. Montgomery, of St. Mary's Hospital in London examined 50 modern British poets. One fourth met current diagnostic criteria for depression or manic-depression; suicide was six times more frequent in this community than in the general population.

Ruth L. Richards and her colleagues at Harvard University set up a system for assessing the degree of original thinking required to perform certain creative tasks. Then, rather than screening for mood disorders among those already deemed highly inventive, they attempted to rate creativity in a sample of manic-depressive patients. Based on their scale, they found that compared with individuals having no personal or family history of psychiatric disorders, manic-depressive and cyclothymic patients (as well as their unaffected relatives) showed greater creativity.

Biographical studies of earlier generations of artists and writers also show consistently high rates of suicide, depression and manic-depression—up to 18 times the rate of suicide seen in the general population, eight to 10 times that of depression and 10 to 20 times that of manic-depressive illness and its milder variants. Joseph J. Schildkraut and his co-workers at Harvard concluded that approximately half of the 15 20th-cen-



LISA BURNETT

INCREASED RATES OF SUICIDE, depression and manic-depression among artists have been established by many separate studies. These investigations show that artists experience up to 18 times the rate of suicide seen in the general population, eight to 10 times the rate of depression and 10 to 20 times the rate of manic-depression and its milder form, cyclothymia.

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tury abstract-expressionist artists they studied suffered from depressive or manic-depressive illness; the suicide rate in this group was at least 13 times the current U.S. national rate.

In 1992 Arnold M. Ludwig of the University of Kentucky published an extensive biographical survey of 1,005 famous 20th-century artists, writers and other professionals, some of whom had been in treatment for a mood disorder. He discovered that the artists and writers experienced two to three times the rate of psychosis, suicide attempts, mood disorders and substance abuse that comparably successful people in business, science and public life did. The poets in this sample had most often been manic or psychotic and hospitalized; they also proved to be some 18 times more likely to commit suicide than is the general public. In a comprehensive biographical study of 36 major British poets born between 1705 and 1805, I found similarly elevated rates of psychosis and severe psychopathology. These poets were 30 times more likely to have had manic-depressive illness than were their contemporaries, at least 20 times more likely to have been committed to an asylum and some five times more likely to have taken their own life.

These corroborative studies have confirmed that highly creative individuals experience major mood disorders more often than do other groups in the general population. But what does this mean for their work? How does a psychiatric illness contribute to creative achievement? First, the common features of hypomania seem highly conducive to original thinking; the diagnostic criteria for this phase of the disorder include "sharpened and unusually creative thinking and increased productivity." And accumulating evidence suggests that the cognitive styles associated with hypomania (expansive thought and grandiose moods) can lead to increased fluency and frequency of thoughts.

Mania and Creativity

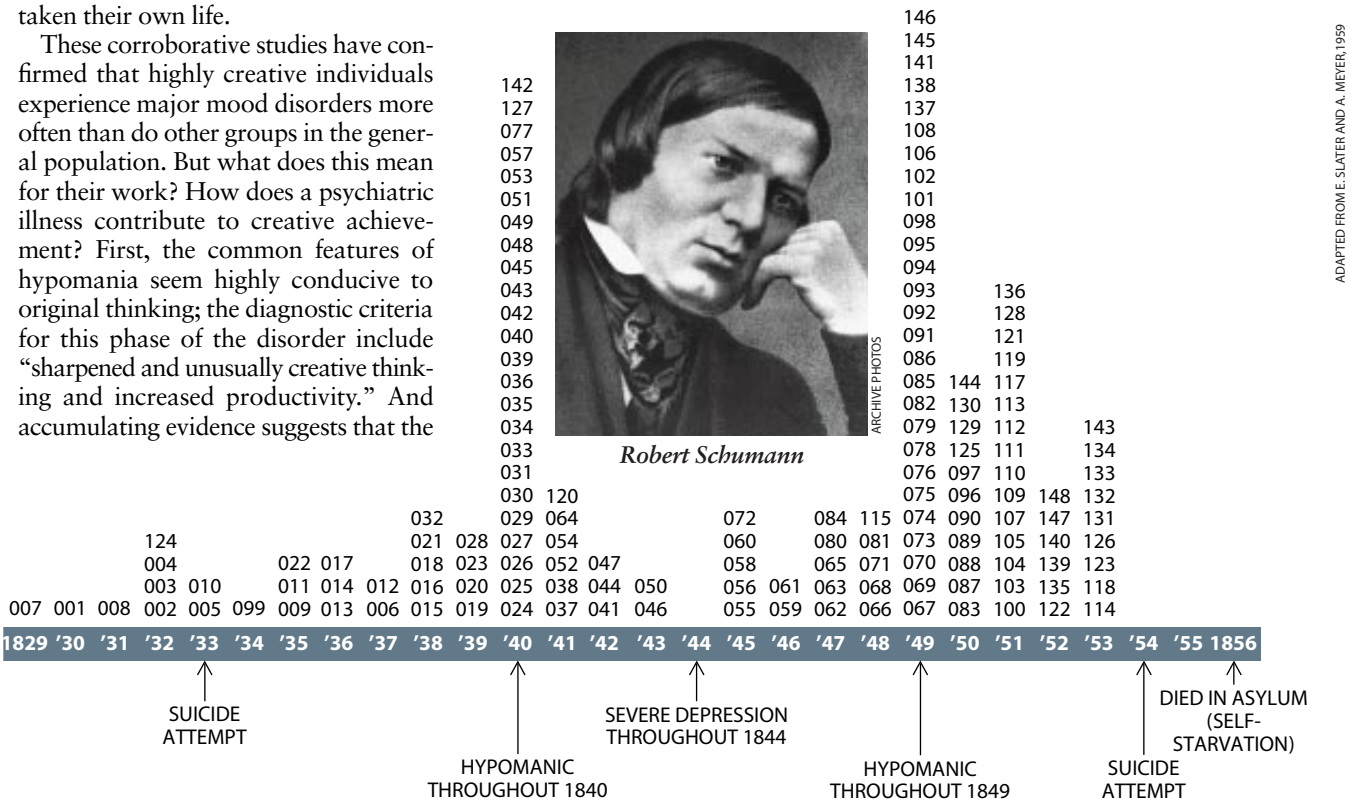
Studying the speech of hypomanic patients has revealed that they tend to rhyme and use other sound associations, such as alliteration, far more often than do unaffected individuals. They also use idiosyncratic words nearly three times as often as do control subjects. Moreover, in specific drills, they can list synonyms or form other word associations much more rapidly than is considered normal. It seems, then, that both the quantity and quality of thoughts build during hypomania. This speed increase may range from a very mild quickening to complete psychotic incoherence. It is not yet clear what causes this qualitative change in mental processing. Nevertheless, this altered cognitive state may well facilitate the formation of unique ideas and associations.

People with manic-depressive illness and those who are creatively accomplished share certain noncognitive features: the ability to function well on a few hours of sleep, the focus needed to work intensively, bold and restless attitudes, and an ability to experience a profound depth and variety of emotions. The less dramatic daily aspects of manic-depression might also provide creative advantage to some individuals. The manic-depressive temperament is, in a biological sense, an alert, sensitive system that reacts strongly and swiftly. It responds to the world with a wide range of emotional, perceptual, intellectual, behavioral and energy changes. In a sense, depression is a view of the world through a dark glass, and mania is that seen through a kaleidoscope—often brilliant but fractured.

Where depression questions, ruminates and hesitates, mania answers with vigor and certainty. The constant transitions in and out of constricted and then expansive thoughts, subdued and then violent responses, grim and then ebullient moods, withdrawn and then outgoing stances, cold and then fiery states—and the rapidity and fluidity of moves through such contrasting experiences—can be painful and confusing. Ideally, though, such chaos in those able to

ARCHIVE PHOTOS

Robert Schumann



ADAPTED FROM E. SLATER AND A. MEYER, 1959

ROBERT SCHUMANN'S MUSICAL WORKS, charted by year and opus number (*above*), **show a striking relation between his mood states and his productivity. He composed the most when hypomanic and the least when depressed. Both of Schumann's parents were clinically depressed, and two other first-degree relatives committed suicide. Schumann himself attempted suicide twice and died in an insane asylum. One of his sons spent more than 30 years in a mental institution.**

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The Case of Vincent van Gogh

Many clinicians have reviewed the medical and psychiatric problems of the painter Vincent van Gogh posthumously, diagnosing him with a range of disorders, including epilepsy, schizophrenia, digitalis and absinthe poisoning, manic-depressive psychosis, acute intermittent porphyria and Ménière's disease.

Richard Jed Wyatt of the National Institute of Mental Health and I have argued in detail that van Gogh's symptoms, the natural course of his illness and his family psychiatric history strongly indicate manic-depressive illness. The extent of the artist's purported use of absinthe and convulsive behavior remains unclear; in any event, his psychiatric symptoms long predate any possible history of seizures. It is possible that he suffered from both an epileptic disorder and manic-depressive illness. —*K. R. J.*

METROPOLITAN MUSEUM OF ART, GIFT OF ADELE R. LEVY, 1958

***Irises*, 1889**

transcend it or shape it to their will can provide a familiarity with transitions that is probably useful in artistic endeavors. This vantage readily accepts ambiguities and the counteracting forces in nature.

Extreme changes in mood exaggerate the normal tendency to have conflicting selves; the undulating, rhythmic and transitional moods and cognitive changes so characteristic of manic-depressive illness can blend or harness seemingly contradictory moods, observations and perceptions. Ultimately, these fluxes and yokings may reflect truth in humanity and nature more accurately than could a more fixed viewpoint. The "consistent attitude toward life" may not, as Byron scholar Jerome J. McGann of the University of Virginia points out, be as insightful as an ability to live with, and portray, constant change.

The ethical and societal implications of the association between mood disorders and creativity are important but poorly understood. Some treatment strategies pay insufficient heed to the benefits manic-depressive illness can bestow on some individuals. Certainly most manic-depressives seek relief from the disease, and lithium and anticonvulsant drugs are very effective therapies for manias and depressions. Nevertheless, these drugs can dampen a person's general intellect and limit his or her emotional and perceptual range. For this reason, many manic-depressive patients stop taking these medications.

Left untreated, however, manic-depressive illness often worsens over time—and no one is creative when severely depressed, psychotic or dead. The attacks of both mania and depression tend to grow more frequent and more severe. Without regular treatment the disease eventually becomes less responsive to medication. In addition, bipolar and unipolar patients frequently abuse mood-altering substances, such as alcohol and illicit drugs, which can cause secondary medical and emotional burdens for manic-depressive and depressed patients.

The Goal of Treatment

The real task of imaginative, compassionate and effective treatment, therefore, is to give patients more meaningful choices than they are now afforded. Useful intervention must control the extremes of depression and psychosis without sacrificing crucial human emotions and experiences. Given time and increasingly sophisticated research, psychiatrists will likely gain a better understanding of the complex biological basis for mood disorders. Eventually, the development of new drugs should make it possible to treat manic-depressive individuals so that those aspects of temperament and cognition that are essential to the creative process remain intact.

The development of more specific and less problematic therapies should be swift once scientists find the gene, or genes, responsible for the disease. Prenatal tests and other diagnostic measures may then become available; these possibilities raise a host of complicated ethical issues. It would be irresponsible to romanticize such a painful, destructive and all too often deadly disease. Hence, 3 to 5 percent of the Human Genome Project's total budget (which is conservatively estimated at $3 billion) has been set aside for studies of the social, ethical and legal implications of genetic research. It is hoped that these investigations will examine the troubling issues surrounding manic-depression and major depression at length. To help those who have manic-depressive illness, or who are at risk for it, must be a major public health priority. SA

Further Reading

TENNYSON: THE UNQUIET HEART. R. B. Martin. Oxford University Press, 1980.

CREATIVITY AND MENTAL ILLNESS: PREVALENCE RATES IN WRITERS AND THEIR FIRST-DEGREE RELATIVES. Nancy C. Andreasen in *American Journal of Psychiatry,* Vol. 144, No. 10, pages 1288-1292; October 1987.

MANIC DEPRESSIVE ILLNESS. Frederick K. Goodwin and Kay R. Jamison. Oxford University Press, 1990.

CREATIVE ACHIEVEMENT AND PSYCHOPATHOLOGY: COMPARISON AMONG PROFESSIONS. Arnold M. Ludwig in *American Journal of Psychiatry,* Vol. 46, No. 3, pages 330–356; July 1992.

TOUCHED WITH FIRE: MANIC-DEPRESSIVE ILLNESS AND THE ARTISTIC TEMPERAMENT. Kay R. Jamison. Free Press/Macmillan, 1993.

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Depression's Double Standard

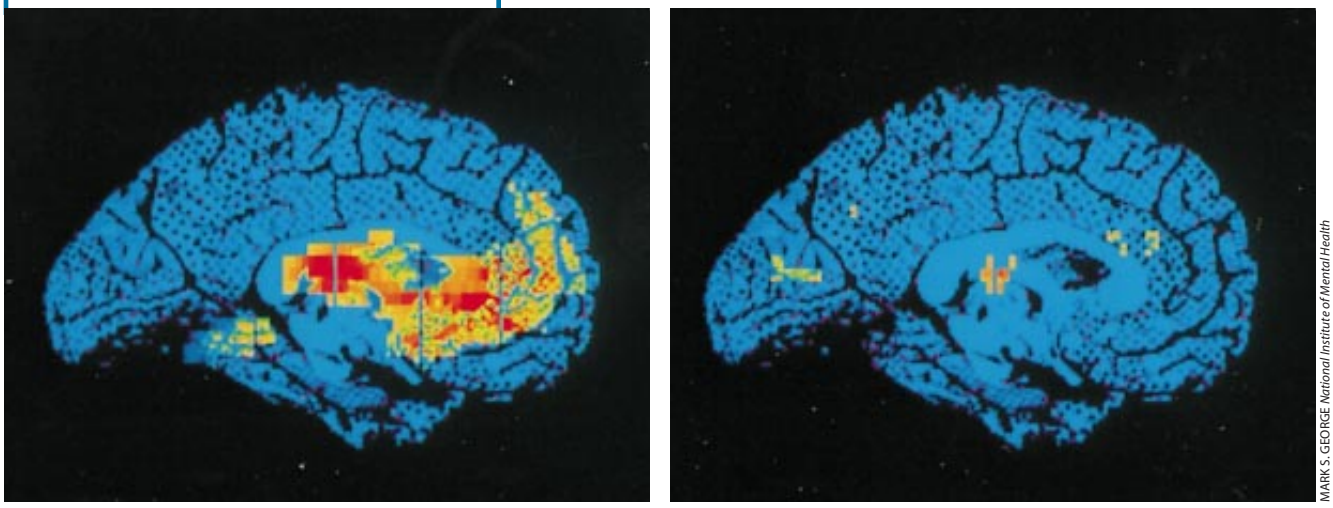
by Kristin Leutwyler, *staff writer*

Studies from 10 nations reveal that the rates of depression among women are twice as high as they are among men. Do women have a biological bent for depression, or are social double standards the major cause?

Mental health workers have long noticed a preponderance of women among the clinically depressed. Until recently, though, it was unclear whether more women than men were ill or, instead, whether more women sought help. In fact, a mounting collection of studies has confirmed that major depression is twice as common among women as it is among men. "This is one of the most consistent findings we have ever had," says Myrna M. Weissman of Columbia University. Women also seem more susceptible to milder melancholia and to seasonal affective disorder (SAD).

Scientists searching for explanations are challenged by the fact that a variety of cues prompt depression in different people. Sorting out which factors might have a greater influence on women has not proved easy. Both sexes stand an equal chance of inheriting major depression, so genes are most likely not to blame. Yet hormones and sleep cycles—which differ dramatically between the sexes—can alter mood. Also, many workers have proposed that social discrimination might put women under high levels of stress, thereby doubly disposing them to major depressive disorder.

In 1990 Weissman and Gerald L. Klerman of Cornell University convened an international group to examine mood disorders. In the 10 nations reviewed so far, the team has found that among generations reaching maturity after 1945, depression seems to be on the rise and occurs at a younger age. Although overall incidence varies regionally, "everywhere the rates of depression among women are about twice as



PET SCANS reveal that during sadness the limbic system in women's brains (*left*) becomes more metabolically active than that area does in men's brains (*right*).

MARK S. GEORGE *National Institute of Mental Health*

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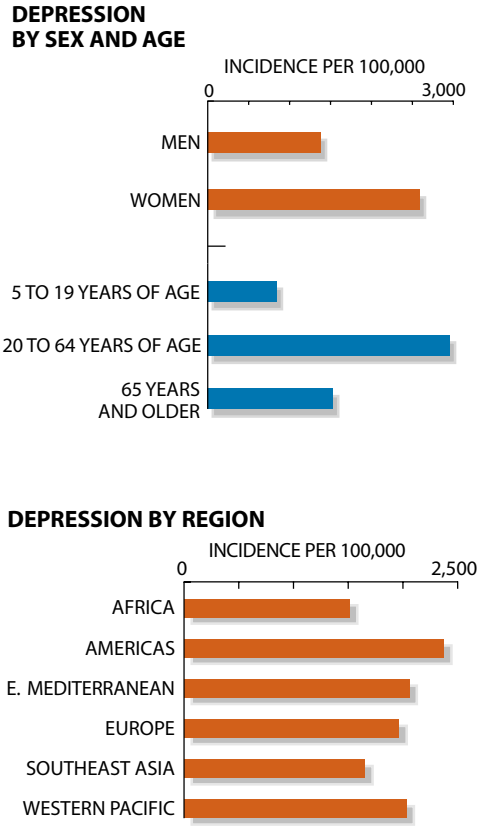

BRYAN CHRISTIE

SOURCE: World Health Organization

INCIDENCE OF DEPRESSION among women worldwide is nearly twice as great as among men (*top*) and less common in the young, according to data gathered by the World Health Organization (WHO). Although incidence of depression in the population varies by region (*middle*), women in every region have substantially higher rates of depression than men. The incidence of depression is highest in economically developed regions and lowest in the least developed nations (*bottom*).

high as they are among men," Weissman says. In contrast, lifetime rates for manic-depressive illness do not differ according to sex or culture.

Meanwhile neurologists and endocrinologists suggest women may well have a biological bent for depression. Mark S. George and his colleagues at the National Institute of Mental Health (NIMH) recently studied which regions of the brain have greater blood flow during periods of sadness. They asked 10 men and 10 women to feel sad while they took a positron emission tomographic (PET) scan. The participants then judged how much sentiment they had mustered. George found that men and women deemed themselves equally sad, but "the brain activity of the two groups looked very different." Both sexes had equally activated the left prefrontal cortex, but the women showed blood flows in the anterior limbic system that were eight times greater. He has since compared feelings of anger, anxiety and happiness, finding no discrepancies anywhere near as large. Most significant, the regions of the brain activated during sadness are two that malfunction during clinical depression. George speculates that hyperactivity of the anterior limbic system in women experiencing sadness could, over time, exhaust that region and lead to the hypoactivity seen there during clinical depression. If he is right, the theory would explain the gender gap, at least in part.

Hormones and Depression

Others at the NIMH have more to add. "There are hints of gender differences in responses both to seasonal patterns and to day and night, or sleep patterns," says Ellen Leibenluft. "Either might put women at a greater risk for depression." Thomas Wehr, also at the NIMH, has found that during the winter, women increase their nightly production of melatonin, a hormone whose levels are governed by the circadian pacemaker; women produce less melatonin during summer nights. In contrast, nocturnal secretions of melatonin in men are unchanging.

Another intriguing find is that without time cues such as daylight, women seem more prone to sleep excessively. (Patients who sleep a great deal during depression are, in fact, those who most often respond to light therapy, Leibenluft says.) Further, sleep and activity cycles are governed by the estrus cycle. Some conjecture that testosterone, which promotes activity, protects men against depression, whereas estrogen may lengthen the sleep phase in women. Gonadal steroids clearly regulate circadian rhythms in animals, and Leibenluft plans to see if they hold similar sway in humans.

George, too, plans to consider the effects of estrogen on brain activation levels during bouts of sadness. Epidemiological data indicate that hormones could play an important role in the onset of depression. Equal numbers of boys and girls experience depression before puberty, but shortly thereafter the rate among girls doubles.

The fact that many depressed patients are women of childbearing age must be considered in research efforts, Leibenluft emphasizes. She notes that although most psychotropic drugs are given to women (75 percent by some estimates), there is little information on how the menstrual cycle might influence their efficacy. Moreover, no one knows how menopause might alter the course of a mood disorder or its treatment. Because one in five American women has a history of depression, many of those who are going through menopause could be affected—especially as they often pursue estrogen replacement therapy, sometimes on top of an antidepressant regime. Says Leibenluft: "It is remarkable how little work has been done on this subject." SA

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The Meaning of Dreams

Dreams may reflect a fundamental aspect of mammalian memory processing. Crucial information acquired during the waking state may be reprocessed during sleep

by Jonathan Winson

The Author

JONATHAN WINSON started his career as an aeronautical engineer, graduating with an engineering degree from the California Institute of Technology in 1946. He completed his Ph.D. in mathematics at Columbia University and then turned to business for 15 years. Because of his keen interest in neuroscience, however, Winson started to do research at the Rockefeller University on memory processing during waking and sleeping states. In 1979 he became an associate professor there and as professor emeritus continues his work on memory and dreaming. His research has been supported by the National Institute of Mental Health, the National Science Foundation and the Harry F. Guggenheim Foundation.

Dreaming occurs solely during REM sleep.

LABAT/JERRICAN *Photo Researchers, Inc.*

Throughout history human beings have sought to understand the meaning of dreams. The ancient Egyptians believed dreams possessed oracular power—in the Bible, for example, Joseph's elucidation of Pharaoh's dream averted seven years of famine. Other cultures have interpreted dreams as inspirational, curative or alternative reality. During the past century, scientists have offered conflicting psychological and neuroscientific explanations for dreams. In 1900, with the publication of *The Interpretation of Dreams,* Sigmund Freud proposed that dreams were the "royal road" to the unconscious; that they revealed in disguised form the deepest elements of an individual's inner life.

More recently, in contrast, dreams have been characterized as meaningless, the result of random nerve cell activity. Dreaming has also been viewed as the means by which the brain rids itself of unnecessary information—a process of "reverse learning," or unlearning.

Based on recent findings in my own and other neuroscientific laboratories, I propose that dreams are indeed meaningful. Studies of the hippocampus (a brain structure crucial to memory), of rapid eye movement (REM) sleep and of a brain wave called theta rhythm suggest that dreaming reflects a pivotal aspect of the processing of memory. In particular, studies of theta rhythm in subprimate animals have provided an evolutionary clue to the meaning of dreams. They appear to be the nightly record of a basic mammalian memory process: the means by which animals form strategies for survival and evaluate current experience in light of those strategies. The existence of this process may explain the meaning of dreams in human beings.

Stages of Sleep and Dreaming

The physiology of dreaming was first understood in 1953, when researchers characterized the human sleep cycle. They found that sleep in humans is initiated by the hypnogogic state, a period of several minutes when thoughts consist of fragmented images or minidramas. The hypnogogic state is followed by slow-wave sleep, so called because at that time the brain waves of the neocortex (the convoluted outer mantle of the brain) are low in frequency and large in amplitude. These signals are measured as electroencephalographic (EEG) recordings.

Researchers also discovered that a night's sleep is punctuated by periods in which the EEG readings are irregular in frequency and low in amplitude—similar to those observed in awake individuals. These periods of mental activity are called REM sleep. Dreaming takes place solely during these periods. While in REM sleep, motor neurons are inhibited, preventing the body from moving freely but allowing extremities to remain slightly active. Eyes

SCALA/ART RESOURCE

JACOB'S LADDER, painted in 1973 by Marc Chagall, depicts a biblical story. Jacob dreams of angels ascending to and descending from heaven on a ladder.

Reprinted from the November 1990 issue

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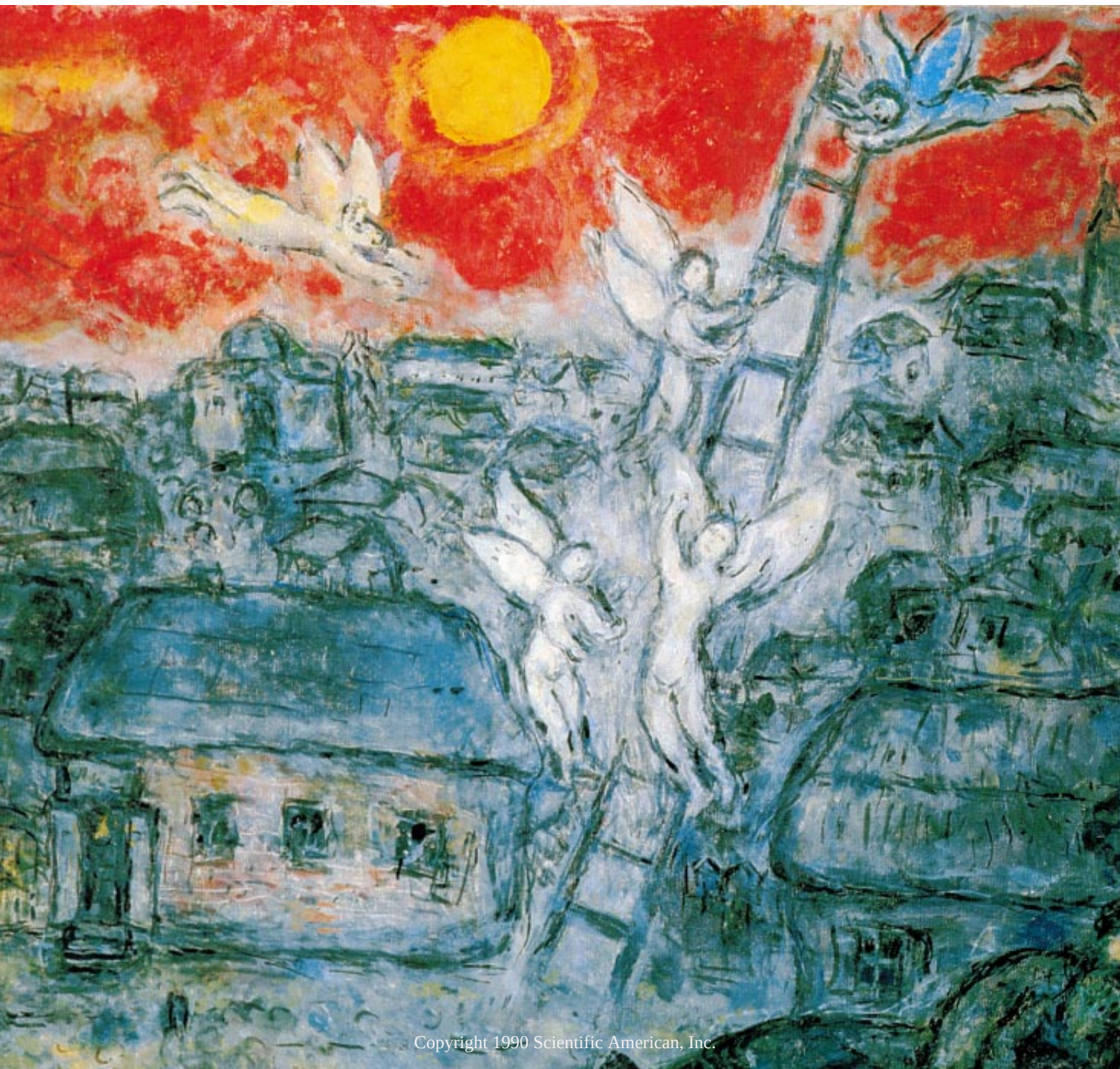
move rapidly in unison under closed lids, breathing becomes irregular and heart rate increases.

The first REM stage of the night follows 90 minutes of slow-wave sleep and lasts for 10 minutes. The second and third REM periods follow shorter slow-wave sleep episodes but grow progressively longer themselves. The fourth and final REM interval lasts 20 to 30 minutes and is followed by awakening. If a dream is remembered at all, it is most often the one that occurred in this last phase of REM sleep.

This sleep cycle—alternating slow-wave and REM sleep—appears to be present in all placental and marsupial mammals. Mammals exhibit the various REM-associated characteristics observed in humans, including EEG readings similar to those of the awake state. Animals also dream. By destroying neurons in the brain stem that inhibit movement during sleep, researchers found that sleeping cats rose up and attacked or were startled by invisible objects—ostensibly images from dreams.

By studying subprimate animals, scientists have discovered additional neurophysiological aspects of REM sleep. They determined that neural control of this stage of the sleep cycle is centered in the brain stem (the brain region closest to the spinal cord) and that during REM sleep neural signals—called pontine-geniculate-occipital (PGO) cortex spikes—proceed from the brain stem to the center of visual processing, the visual cortex. Brain stem neurons also initiate a sinusoidal wave (one resembling a sine curve) in the hippocampus. This brain signal is called theta rhythm.



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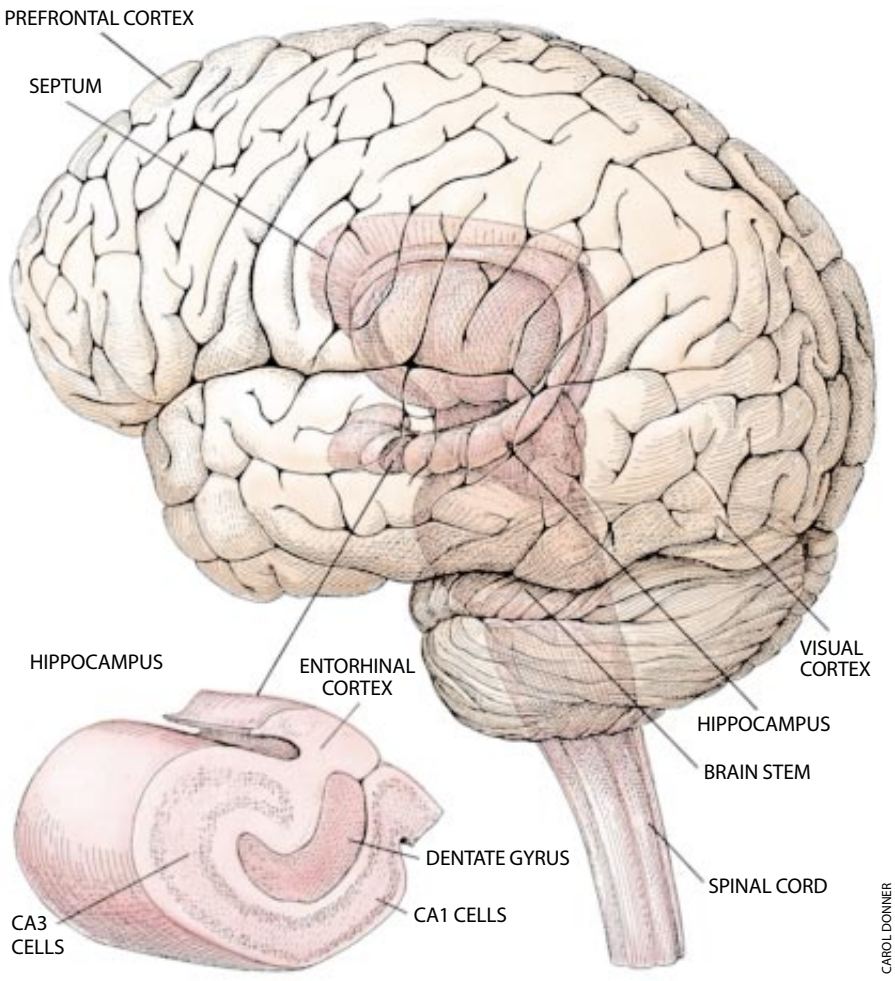

ANATOMY OF THE BRAIN and cross section of the hippocampus show some of the regions involved in dreaming. In the hippocampus, incoming information is processed sequentially in the dentate gyrus and the CA3 and the CA1 pyramidal cells. In subprimate species, theta rhythm is generated in the dentate gyrus and the CA1 cells.

At least one animal experiences slow-wave but not REM sleep—and, consequently, does not exhibit theta rhythm when asleep. This animal is the echidna, or spiny anteater, an egg-laying mammal (called a monotreme) that provides some insight into the origin of dreaming. The absence of REM sleep in the echidna suggests that this stage of the sleep cycle evolved some 140 million years ago, when marsupials and placentals diverged from the monotreme line. (Monotremes were the first mammals to develop from reptiles.)

By all evolutionary criteria, the perpetuation of a complex brain process such as REM sleep indicates that it serves an important function for the survival of mammalian species. Understanding that function might reveal the meaning of dreams.

When Freud wrote *The Interpretation of Dreams,* the physiology of sleep was unknown. In light of the discovery of REM sleep, certain elements of his psychoanalytic theory were modified, and the stage was set for more neurologically based theories. Dreaming came to be understood as part of a biologically determined sleep cycle. Yet the central concept of Freud's theory—namely, the belief that dreams reveal a censored representation of our innermost unconscious feelings and concerns—continues to be used in psychoanalysis.

Some theorists abandoned Freud altogether following the neurological discoveries. In 1977 J. Allan Hobson and Robert McCarley of Harvard Medical School proposed the "activation-synthesis" hypothesis. They suggested that dreaming consists of associations and memories elicited from the forebrain (the neocortex and associated structures) in response to random signals from the brain stem such as PGO spikes. Dreams were merely the "best fit" the forebrain could provide to this random bombardment from the brain stem. Although dreams might at times appear to have psychological content, their bizarreness was inherently meaningless.

The sense, or plot, of dreams resulted from order that was imposed on the chaos of neural signals, Hobson said. "That order is a function of our own personal view of the world, our remote memories," Hobson wrote. In other words, the individual's emotional vocabulary could be relevant to dreams. In a further revision of the original hypothesis, Hobson also suggested that brain stem activation may merely serve to switch from one dream episode to another.

Reverse Learning

Although Hobson and McCarley had presented an explanation of dream content, the basic function of REM sleep admittedly remained unknown. In 1983 Francis Crick of the Salk Institute in La Jolla, Calif., and Graeme Mitchison of the University of Cambridge in England proposed the idea of reverse learning. Working from the Hobson-McCarley assumption of random neocortical bombardment by PGO waves and their own knowledge of the behavior of stimulated neural networks, they postulated that a complex associational neural network such as the neocortex might become overloaded by vast amounts of incoming information. The neocortex could then develop false, or "parasitic," thoughts that would jeopardize the true and orderly storage of memory.

According to Crick and Mitchison's hypothesis, REM sleep served to erase these spurious associations on a regular basis. Random PGO waves impinged on the neocortex, resulting in erasure, or unlearning, of the false information. This process served an essential function: it allowed the orderly processing of memory. In humans, dreams were a running record of these parasitic thoughts—material to be purged from memory. "We dream to forget," Crick and Mitchison wrote.

The two researchers proposed a revision in 1986. Erasure of parasitic thoughts accounted only for bizarre dream content. Nothing could be said about dream narrative. Furthermore, dreaming to forget, they said, was better expressed as dreaming to reduce fantasy or obsession.

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None of these hypotheses seems to explain adequately the function of dreaming. On the one hand, Freud's theory lacked physiological evidence. (Although Freud had originally intended to describe the neurology of the unconscious and of dreams in his proposed "Project for a Scientific Psychology," the undertaking was premature, and he limited himself to psychoanalysis.) On the other hand, despite revisions to incorporate elements of psychology, most of the later theories denied that dreams had meaning.

Exploring the neuroscientific aspects of REM sleep and of memory processing seemed to me to hold the greatest potential for understanding the meaning and function of dreams. The key to this research was theta rhythm.

Theta rhythm was discovered in 1954 in awake animals by John D. Green and Arnaldo A. Arduini of the University of California at Los Angeles. The researchers observed a regular sinusoidal signal of six cycles per second in the hippocampus of rabbits when the animals were apprehensive of stimuli in their environment. They named the signal theta rhythm after a previously discovered EEG component of the same frequency.

Theta rhythm was subsequently recorded in the tree shrew, mole, rat and cat. Although it was consistently observed in awake animals, theta rhythm was correlated with very different behaviors in each species. For example, in marked contrast to the rabbit, environmental stimuli did not induce theta rhythm in the rat. Rats demonstrated theta rhythm only during movement, typically when they explored. In 1969, however, Case H. Vanderwolf of the University of Western Ontario discovered there was one behavior during which the animals he studied, including the rat, showed theta rhythm: REM sleep.

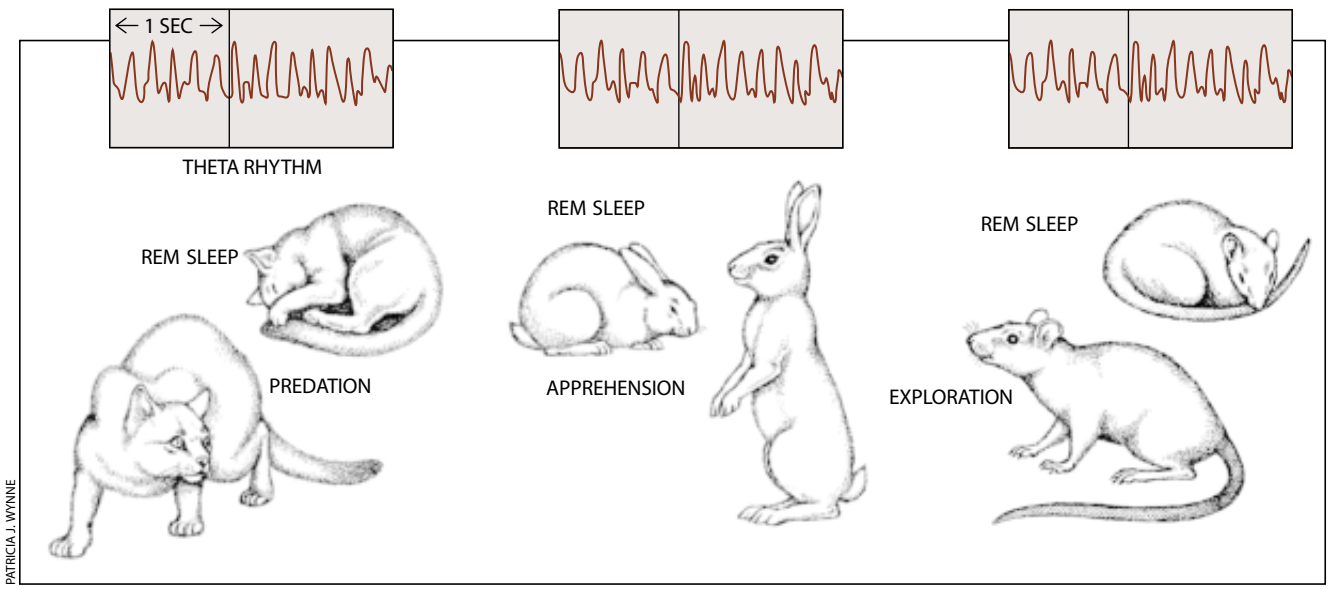
In 1972 I published a commentary pointing out that the different occurrences of theta rhythm could be understood in terms of animal behavior. Awake animals seemed to show theta rhythm when they were behaving in ways most crucial to their survival. In other words, theta rhythm appeared when they exhibited behavior that was not genetically encoded—such as feeding or sexual behavior—but rather a response to changing environmental information. Predatory behavior in the cat, prey behavior in the rabbit, and exploration in the rat are, respectively, most important to their survival. (For example, a hungry rat will explore before it eats even if food is placed in front of it.)

Role of Theta Rhythm

Furthermore, because the hippocampus is involved in memory processing, the presence of theta rhythm during REM sleep in that region of the brain might be related to that activity. I suggested that the theta rhythm reflected a neural process whereby information essential to the survival of a species—gathered during the day—was reprocessed into memory during REM sleep.

In 1974, by recording signals from the hippocampus of freely moving rats and rabbits, I found the source from which theta rhythm was generated in the hippocampus. Together with the neocortex, the hippocampus is believed to provide the neural basis for memory storage. The hippocampus (from the Greek word for "seahorse," which it resembles in shape) is a sequential structure composed of three types of neurons. Information from all sensory and associational areas of the neocortex converges in a region called the entorhinal cortex; from there it is transmitted to the three successive neuronal populations of the hippocampus. The signal arrives first at the granule cells of the dentate gyrus, then at the CA3 pyramidal cells (so called because of their triangular shape) and finally at the pyramidal cells of CA1. After information is processed by this trio of cells, it is retransmitted to the entorhinal cortex and then back to the neocortex.

My studies showed that theta rhythm was produced in two regions within the hippocampus: the dentate gyrus and the CA1 neurons. The rhythms in these two areas were synchronous. Subsequently, Susan Mitchell and James B. Ranck, Jr., of the State University of New York Downstate Medical Center identified a third synchronous generator in the entorhinal cortex, and Robert Verdes of Wayne State University discovered the brain stem neurons that control theta rhythm. These neurons transmit signals to the septum (a forebrain structure) that activate theta rhythm in the hippo-



THETA RHYTHM is present during different waking behaviors in different species. Each of these behaviors is pivotal to the animal's survival. In placental and marsupial animals, theta rhythm is present during rapid eye movement (REM) sleep.

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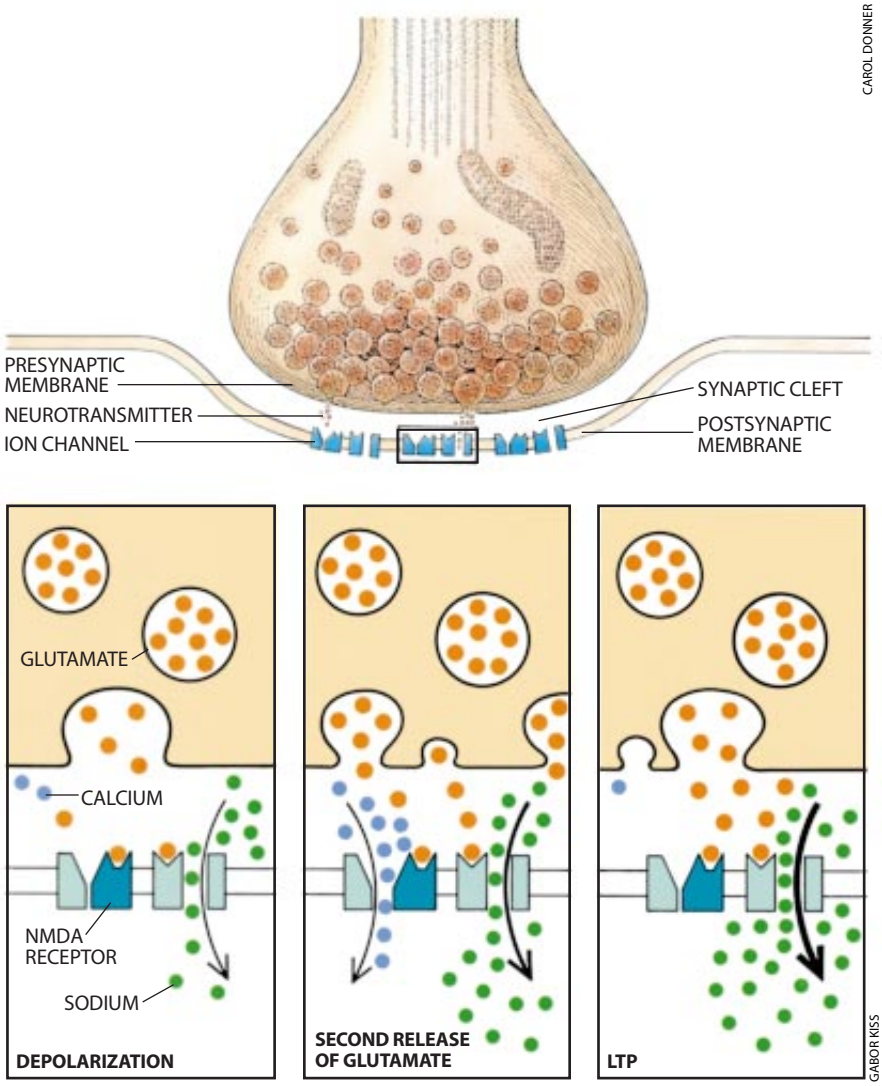

NMDA RECEPTOR activation induces long-term potentiation (LTP), a model for memory. The release of the neurotransmitter glutamate (*left panel*) opens a non–NMDA receptor channel, allowing the influx of sodium, which depolarizes the neuron. If a further release of glutamate occurs while the cell is depolarized (*center panel*), the NMDA receptor opens a second channel, which allows calcium to flow in, leading to LTP. LTP occurs as a result of increased sodium through the non-NMDA channel (*right panel*) and the subsequent greater depolarization of the cell.

campus and the entorhinal cortex. Thus, the brain stem activates the hippocampus and the neocortex—the core memory system of the brain.

To determine the relation between theta rhythm and memory, I made a lesion in the rat septum. Rats that had previously learned, using spatial cues, to locate a particular position in a maze were no longer able to do so after their septums were disabled. Without theta rhythm, spatial memory was destroyed.

Studies of the cellular changes that bring about memory illustrated the role of theta rhythm. In particular, the discovery in 1973 of long-term potentiation (LTP)—a change in neural behavior that reflects previous activity—showed the means by which memory might be encoded. Timothy V. P. Bliss and A. R. Gardner-Medwin of the National Institute of Medical Research in London and Terje Lømo of the University of Oslo found changes in nerve cells that had been intensely stimulated with electrical pulses.

Long-Term Memory Storage

Earlier studies had shown that if one stimulated the pathway from the entorhinal cortex to the granule cells of the hippocampus, the response of these cells could be measured with a recording electrode. Using this technique, Bliss and his colleagues measured the normal response to a single electrical pulse. Then they applied a long series of high-frequency signals—called tetanic pulses—to this pathway. After the train of tetanic stimuli, a single electrical pulse caused much greater firing in the granule cells than had been observed prior to the experiment. The heightened effect persisted for as long as three days. This phenomenon of LTP was precisely the kind of increase in neuronal strength that could be capable of sustaining memory. LTP is now considered a model for learning and memory.

LTP is achieved by the activity of the NMDA (*N*-methyl-D-aspartate) receptor. This molecule is embedded in the dendrites of the granule cells and the CA1 cells of the hippocampus as well as in neurons throughout the neocortex. Like other neuronal receptors, the NMDA receptor is activated by a neurotransmitter—glutamate in this case. Glutamate momentarily opens a non-NMDA channel in the granule cell dendrite, allowing sodium from the extracellular space to flow into the neuron. This influx causes the granule cell to become depolarized. If the depolarization is sufficient, the granule cell fires, transmitting information to other nerve cells.

Unlike other neuronal receptors, NMDA possesses an additional property. If a further activation of glutamate occurs while the granule cell is depolarized, a second channel opens up, allowing an influx of calcium. Calcium is thought to act as a second messenger, initiating a cascade of intracellular events that culminates in long-lasting synaptic changes—or LTP. (The description given here has been necessarily simplified. LTP is the subject of extensive ongoing investigation.)

Because the tetanic impulses applied by Bliss and his colleagues did not occur naturally in the brain, the question remained as to how LTP was achieved under normal circumstances. In 1986 John Larson and Gary S. Lynch of the University of California at Irvine and Gregory Rose and Thomas V. Dunwiddie of the University of Colorado at Denver suggested that the occurrence of LTP in the hippocampus was linked to theta rhythm. They applied a small number of electrical pulses to CA1 cells in the rat hippocampus and produced LTP, but only when the pulses were separated by the normal time that elapses between two theta waves—approximately

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200 milliseconds. Theta rhythm is apparently the natural means by which the NMDA receptor is activated in neurons in the hippocampus.

Work in my laboratory at the Rockefeller University duplicated Larson and Lynch's CA1 findings, but this time in the hippocampal granule cells. Constantine Pavlides, Yoram J. Greenstein and I then demonstrated that LTP was dependent on the presence and phase of theta rhythm. If electrical pulses were applied to the cells at the peak of the theta wave, LTP was induced. But if the same pulse were applied at the trough of the waves—or when theta rhythm was absent—LTP was not induced.

A coherent picture of memory processing was emerging. As a rat explores, for example, brain stem neurons activate theta rhythm. Olfactory input (which in the rat is synchronized with theta rhythm, as is the twitching of whiskers) and other sensory information converge on the entorhinal cortex and the hippocampus. There they are partitioned into 200-millisecond "bites" by theta rhythm. The NMDA receptors, acting in conjunction with theta rhythm, allow for long-term storage of this information.

A similar process occurs during REM sleep. Although there is no incoming information or movement during REM sleep, the neocortical-hippocampal network is once again paced by theta rhythm. Theta rhythm might produce long-lasting changes in memory.

Storing Spatial Memory

The results of one of my further experiments served to show that spatial memory was indeed being stored in the rat hippocampus during sleep. John O'Keefe and J. Dostrovsky of the University College London had demonstrated that individual CA1 neurons in the rat hippocampus fired when the awake animal moved to a particular location—namely, the neuron's place field. The implication of this finding was that the CA1 neuron fired to map the environment, thereby committing it to memory.

In 1989 Pavlides and I located two CA1 neurons in the rat hippocampus that had different place fields. We recorded from both cells simultaneously. After determining the normal firing rates in awake and asleep animals, we positioned a rat in the place field of one of the neurons. The neuron fired vigorously, mapping that location. The second cell fired only sporadically because it was not coding space. We continued recording from the two pairs of neurons as the rat moved about and then entered several sleep cycles. Six pairs of neurons were studied in this manner.

We found that neurons that had coded space fired at a normal rate as the animal moved about prior to sleep. In sleep, however, they fired at a significantly higher rate than their previous sleeping baseline. There was no such increase in firing rate during sleep in neurons that had not mapped space. This experiment suggested that the reprocessing or strengthening of information encoded when the animal was awake occurred in sleep at the level of individual neurons.

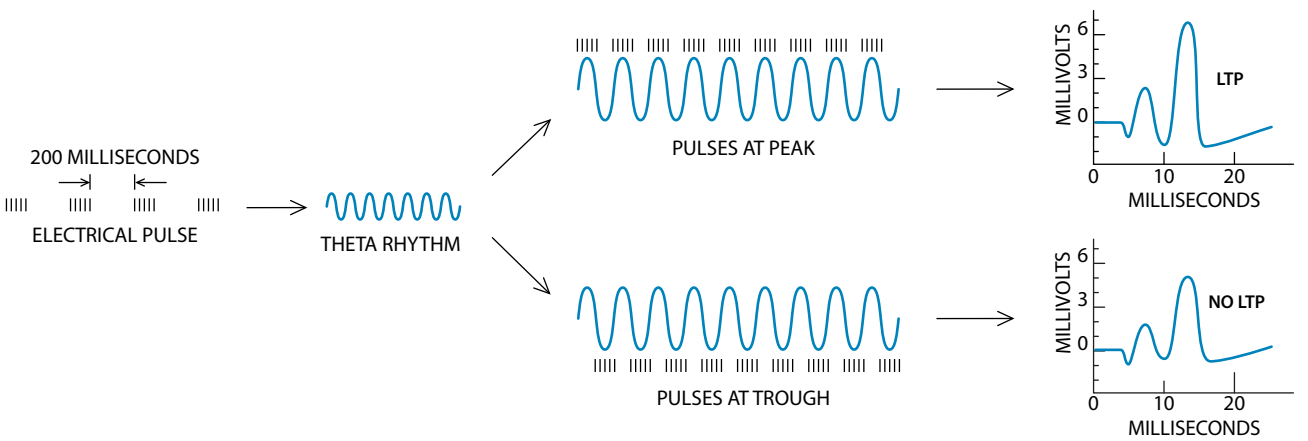
Bruce L. McNaughton and his colleagues at the University of Arizona have developed a technique for simultaneously recording from a large number of neurons in the hippocampus that map locations. Their technique allows definitive patterns of firing to be identified. In animal studies, they found that ensembles of place-field neurons that code space in the waking state reprocess information during slow-wave sleep and then in REM sleep. These results suggest that sleep processing of memory may have two stages—a preliminary stage in slow-wave sleep and a later phase in REM sleep, when dreaming occurs.

Evolution of REM Sleep

Evidence that theta rhythm encodes memories during REM sleep may be derived not only from neuroscientific studies but also from evolution. The emergence of a neural mechanism to process memory in REM sleep suggests differences in brain anatomy between mammals that have that aspect of the sleep cycle and those that do not. And in fact, such differences clearly exist between the echidna and the marsupials and placentals.

The echidna has a large convoluted prefrontal cortex, larger in relation to the rest of the brain than that of any other mammal, even humans. I believe it needed this huge prefrontal cortex to perform a dual function: to react to incoming information in an appropriate manner based on past experience and to evaluate and store new information to aid in future survival. Without theta rhythm during REM sleep, the echidna would not be able to process information while it slept. (The echidna does, however, show theta rhythm when foraging for food.) For higher capabilities to develop, the prefrontal cortex would have to become increasingly large—beyond the capacity of the skull—unless another brain mechanism evolved.

REM sleep could have provided this new mechanism, allowing memory processing to occur "off-line." Coincident with the apparent development of REM



GABOR KISS

LTP in the granule cells of the hippocampus is achieved by theta rhythm. Electrical pulses, which have been separated by 200 milliseconds (the time between the peaks of two theta waves), result in LTP when applied at the peak of theta rhythm.

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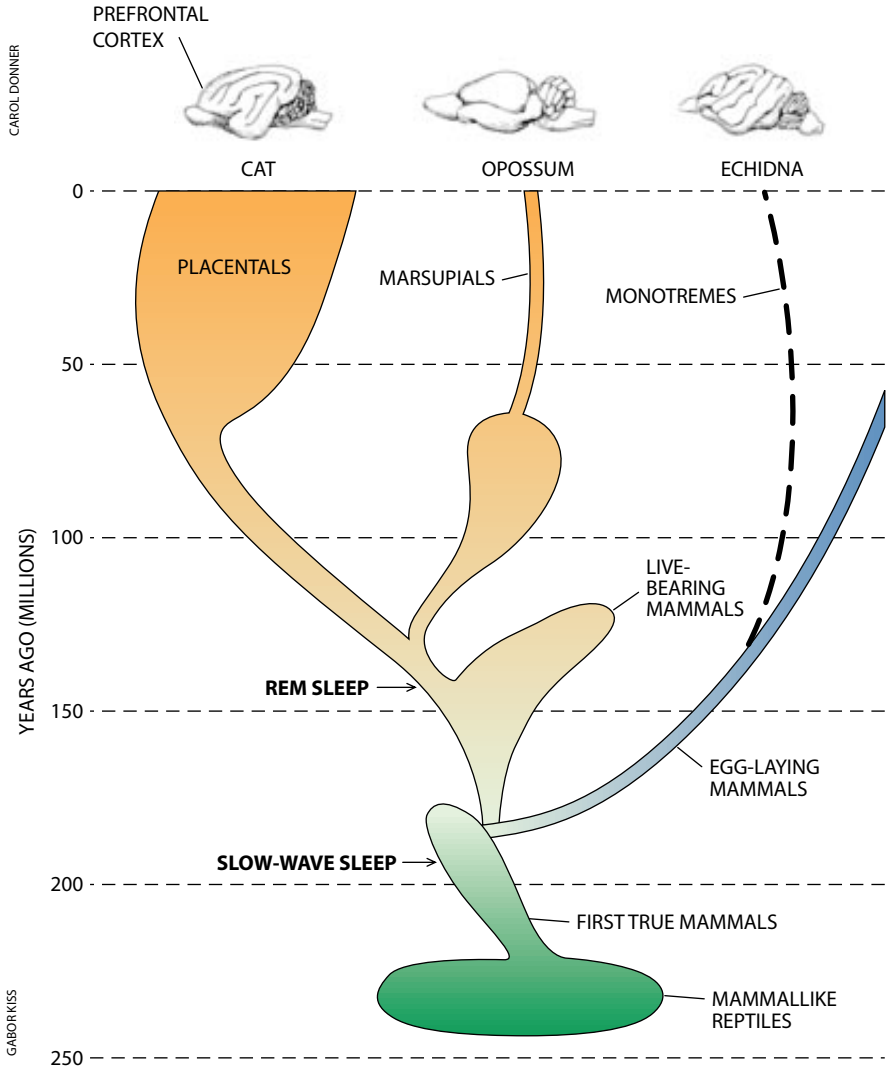

EVOLUTIONARY TREE shows the divergence of placentals and marsupials from monotremes. The echidna, which does not possess REM sleep, has a larger prefrontal cortex compared with the rest of its brain than does any mammal, even humans. It is larger than in similarly sized animals, including the opossum and cat.

sleep in marsupial and placental mammals was a remarkable neuroanatomical change: the prefrontal cortex was dramatically reduced in size. Far less prefrontal cortex was required to process information. That area of the brain could develop to provide advanced perceptual abilities in higher species.

The nature of REM sleep supports this evolutionary argument. During the day, animals gather information that involves locomotion and eye movement. The reprocessing of this information during REM sleep would not be easily separated from the locomotion related to the experience—such disassociation might be expecting too great a revision of brain circuitry. So to maintain sleep, locomotion had to be suppressed by inhibiting motor neurons. Suppressing eye movement was unnecessary because this activity does not disturb sleep.

Eye movement potentials, similar to PGO spikes, accompany rapid eye movement in the waking state and also during REM sleep. The function of these signals has not yet been established, but they may serve to alert the visual cortex to incoming information when the animal is awake and may reflect the reprocessing of this information during REM sleep. In any case, PGO spikes do not disturb sleep and do not have to be suppressed—unlike motor neurons.

Strategy for Survival

With the evolution of REM sleep, each species could process the information most important for its survival, such as the location of food or the means of predation or escape—those activities during which theta rhythm is present. In REM sleep this information may be accessed again and integrated with past experience to provide an ongoing strategy for behavior. Although theta rhythm has not yet been demonstrated in primates, including humans, the brain signal provides a clue to the origin of dreaming in humans. Dreams may reflect a memory-processing mechanism inherited from lower species, in which information important for survival is reprocessed during REM sleep. This information may constitute the core of the unconscious.

Because animals do not possess language, the information they process during REM sleep is necessarily sensory. Consistent with our early mammalian origins, dreams in humans are sensory, primarily visual. Dreams do not take the form of verbal narration.

Also in keeping with the role REM sleep played in processing memories in animals, there is no functional necessity for this material to become conscious. Consciousness arose later in evolution in humans. But neither is there any reason for the material of dreams not to reach consciousness. Therefore, dreams can be remembered—most readily if awakening occurs during or shortly after a REM sleep period.

Consistent with evolution and evidence derived from neuroscience and reports of dreams, I suggest that dreams reflect an individual's strategy for survival. The subjects of dreams are broad-ranging and complex, incorporating self-image, fears, insecurities, strengths, grandiose ideas, sexual orientation, desire, jealousy and love.

Dreams clearly have a deep psychological core. This observation has been reported by psychoanalysts since Freud and is strikingly illustrated by the work of Rosalind Cartwright of Rush-Presbyterian–St. Luke's Hospital in Chicago. Cartwright is studying a series of 90 subjects who are undergoing marital separation and divorce. All the subjects are clinically evaluated and psychologically tested to ascertain their attitudes and responses to their personal crisis. Cartwright's subjects are also awakened from REM sleep to report their dreams,

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which are then interpreted by the subjects themselves without questions that might influence their interpretation. In the 70 individuals studied to date, the dream content conveys the person's unconscious thoughts and is strongly correlated with the manner in which he or she is coping with the crisis while awake.

Although the topic "chosen" for consideration during a night's sleep is unpredictable, certain of life's difficulties—as in the case of Cartwright's subjects—so engage psychological survival that they are selected for REM sleep processing. In the ordinary course of events, depending on the individual's personality, the themes of dreams may be freewheeling. Moreover, when joined with the intricate associations that are an intrinsic part of REM sleep processing, the dream's statement may be rather obscure.

Nevertheless, there is every reason to believe that the cognitive process taking place in Cartwright's subjects occurs in every individual. Interpretation of the coherent statement that is being made depends on the individual's tracing of relevant or similar events. These associations are strongly biased toward early childhood experience.

My hypothesis also offers an explanation for the large amount of REM sleep in infants and children. Newborns spend eight hours a day in REM sleep. The sleep cycle is disorganized at this age. Sleep occurs in 50- to 60-minute bouts and begins with REM rather than with slow-wave sleep. By the age of two, REM sleep is reduced to three hours a day, and the adult pattern has been established. Thereafter, the time spent in REM sleep gradually diminishes to a little less than two hours.

REM sleep may perform a special function in infants. A leading theory proposes that it stimulates nerve growth. Whatever the purpose in infants may be, I suggest that at about the age of two, when the hippocampus, which continues to develop after birth, becomes functional, REM sleep takes on its interpretive memory function. The waking information to be integrated at this point in development constitutes the basic cognitive substrate for memory—the concept of the real world against which later experiences must be compared and interpreted. The organization in memory of this extensive infrastructure requires the additional REM sleep time.

For reasons he could not possibly have known, Freud set forth a profound truth in his work. There is an unconscious, and dreams are indeed the "royal road" to its understanding. The characteristics of the unconscious and associated processes of brain functioning, however, are very different from what Freud thought. Rather than being a cauldron of untamed passions and destructive wishes, I propose that the unconscious is a cohesive, continually active mental structure that takes note of life's experiences and reacts according to its own scheme of interpretation. Dreams are not disguised as a consequence of repression. Their unusual character is a result of the complex associations that are culled from memory.

Memory Consolidation

Research on REM sleep suggests that there is a biologically relevant reason for dreaming. The revised version of the Hobson-McCarley activation-synthesis hypothesis acknowledges the deep psychological core of dreams. In its present truncated form, the hypothesis of random brain stem activation has little explanatory or predictive power.

The Crick-Mitchison hypothesis provides a function for REM sleep—reverse learning—but it does not apply to narrative, only to the bizarre elements of the dream. What this implies with regard to REM processing in lower species must be defined before the theory can be evaluated further. In addition, the Crick-Mitchison hypothesis as applied to the hippocampus would suggest that neurons fire randomly during REM sleep, providing reverse learning. Instead, in my experiment on the neurons that coded space, these neurons fired selectively, implying an orderly processing of memory.

Recently Avi Karni and his colleagues at the Weizmann Institute of Science in Israel were able to show that memory processing occurs in humans during REM sleep. In their experiment, individuals learned to identify particular patterns on a screen. The memory of this skill improved after a night with REM sleep. When the subjects were deprived of REM sleep, memory consolidation did not occur. This study is an important breakthrough and opens a particularly promising field for exploration.

Further study will continue to elucidate the meaning of dreams. In particular, an experiment is needed to determine whether eliminating theta rhythm during REM sleep alone results in a memory deficit. Because theta rhythm has not been demonstrated in primates, it may have disappeared as vision replaced olfaction as the dominant sense. An equivalent neural mechanism may exist in the hippocampus that periodically activates the NMDA receptor. These studies in animals and others to come in humans will probe fundamental aspects of memory processing and the neuroscientific basis of human psychological structure. SA

Further Reading

INTERSPECIES DIFFERENCES IN THE OCCURRENCE OF THETA. Jonathan Winson in *Behavioral Biology,* Vol. 7, No. 4, pages 479–487; 1972.

LOSS OF HIPPOCAMPAL THETA RHYTHM RESULTS IN SPATIAL MEMORY DEFICIT IN THE RAT. Jonathan Winson in *Science,* Vol. 201, No. 435, pages 160–163; 1978.

BRAIN AND PSYCHE: THE BIOLOGY OF THE UNCONSCIOUS. Jonathan Winson. Anchor Press, Doubleday, 1985.

LONG-TERM POTENTIATION IN THE DENTATE GYRUS IS INDUCED PREFERENTIALLY ON THE POSITIVE PHASE OF Q-RHYTHM. Constantine Pavlides, Yoram J. Greenstein, Mark Grudman and Jonathan Winson in *Brain Research,* Vol. 439, pages 383–387; 1988.

INFLUENCES OF HIPPOCAMPAL PLACE CELL FIRING IN THE AWAKE STATE ON THE ACTIVITY OF THESE CELLS DURING SUBSEQUENT SLEEP EPISODES. Constantine Pavlides and Jonathan Winson in *Journal of Neuroscience,* Vol. 9, No. 8, pages 2907–2918; August, 1989.

DEPENDENCE ON REM SLEEP OF OVERNIGHT IMPROVEMENT OF A PERCEPTUAL SKILL. Avi Karni, David Tanne, Barton S. Rubenstein, Jean J. M. Askenasy and Dov Sagi in *Science,* Vol. 265, pages 679–682; July 29, 1994.

REACTIVATION OF HIPPOCAMPAL ENSEMBLE MEMORIES DURING SLEEP. Mathew A. Wilson and Bruce L. McNaughton in *Science,* Vol. 265, pages 676–679; July 29, 1994.

REM SLEEP AND THE REACTIVATION OF RECENT CORRELATION PATTERNS IN HIPPOCAMPAL NEURONAL ENSEMBLES. H. S. Kudrimoto, W. F. Skaggs, C. A. Barnes, B. L. McNaughton, J. L. Gerrard, M. S. Suster and K. L. Weaver in *Society for Neuroscience Abstracts,* page 1871; 1996.

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Emotion, Memory and the Brain

The neural routes underlying the formation of memories about primitive emotional experiences, such as fear, have been traced

by Joseph E. LeDoux

The Author

JOSEPH E. LEDOUX is interested in the neural foundation of memory and emotion. He studies the anatomy, physiology and behavioral organization of these aspects of mental functioning. LeDoux, the Henry and Lucy Moses Professor of Science at New York University, is the recipient of two National Institute of Mental Health distinctions: a Merit Award and a Research Scientist Development Award. He has also received an Established Investigator Award from the American Heart Association.

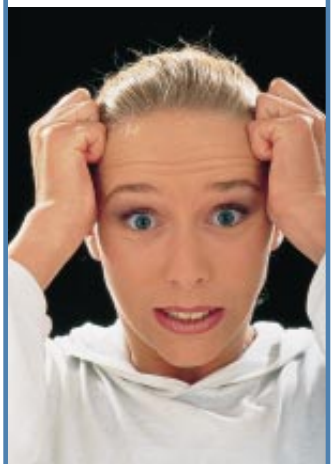
Despite millennia of preoccupation with every facet of human emotion, we are still far from explaining in a rigorous physiological sense this part of our mental experience. Neuroscientists have, in modern times, been especially concerned with the neural basis of such cognitive processes as perception and memory. They have for the most part ignored the brain's role in emotion. Yet in recent years, interest in this mysterious mental terrain has surged. Catalyzed by breakthroughs in understanding the neural basis of cognition and by an increasingly sophisticated knowledge of the anatomical organization and physiology of the brain, investigators have begun to tackle the problem of emotion.

One quite rewarding area of research has been the inquiry into the relation between memory and emotion. Much of this examination has involved studies of one particular emotion—fear—and the manner in which specific events or stimuli come, through individual learning experiences, to evoke this state. Scientists, myself included, have been able to determine the way in which the brain shapes how we form memories about this basic, but significant, emotional event. We call this process "emotional memory."

By uncovering the neural pathways through which a situation causes a creature to learn about fear, we hope to elucidate the general mechanisms of this form of memory. Because many human mental disorders—including anxiety, phobia, post-traumatic stress syndrome and panic attack—involve malfunctions in the brain's ability to control fear, studies of the neural basis of this emotion may help us further understand and treat these disturbances.

Most of our knowledge about how the brain links memory and emotion has been gleaned through the study of so-called classical fear conditioning. In this process the subject, usually a rat, hears a noise or sees a flashing light that is paired with a brief, mild electric shock to its feet. After a few such experiences, the rat responds automatically to the sound or light, even in the absence of the shock. Its reactions are typical to any threatening situation: the animal freezes, its blood pressure and heart rate increase, and it startles easily. In the language of such experiments, the noise or flash is a conditioned stimulus, the foot shock is an unconditioned stimulus, and the rat's reaction is a conditioned response, which consists of readily measured behavioral and physiological changes.

Memories of disturbing experiences form deep within our brains.



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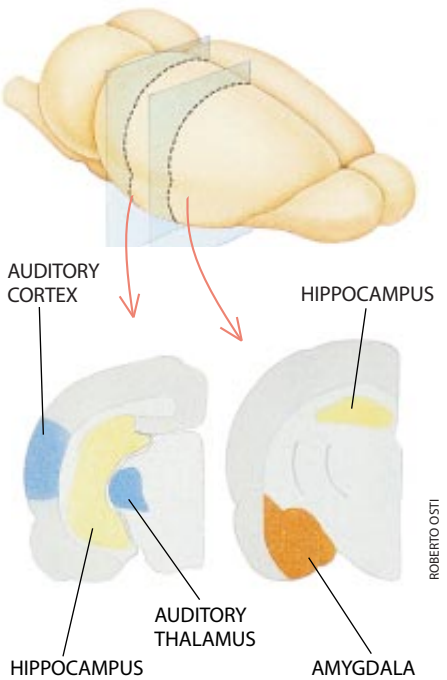
Conditioning of this kind happens quickly in rats—indeed, it takes place as rapidly as it does in humans. A single pairing of the shock to the sound or sight can bring on the conditioned effect. Once established, the fearful reaction is relatively permanent. If the noise or light is administered many times without an accompanying electric shock, the rat's response diminishes. This change is called extinction. But considerable evidence suggests that this behavioral alteration is the result of the brain's controlling the fear response rather than the elimination of the emotional memory. For example, an apparently extinguished fear response can recover spontaneously or can be reinstated by an irrelevant stressful experience. Similarly, stress can cause the reappearance of phobias in people who have been suc-



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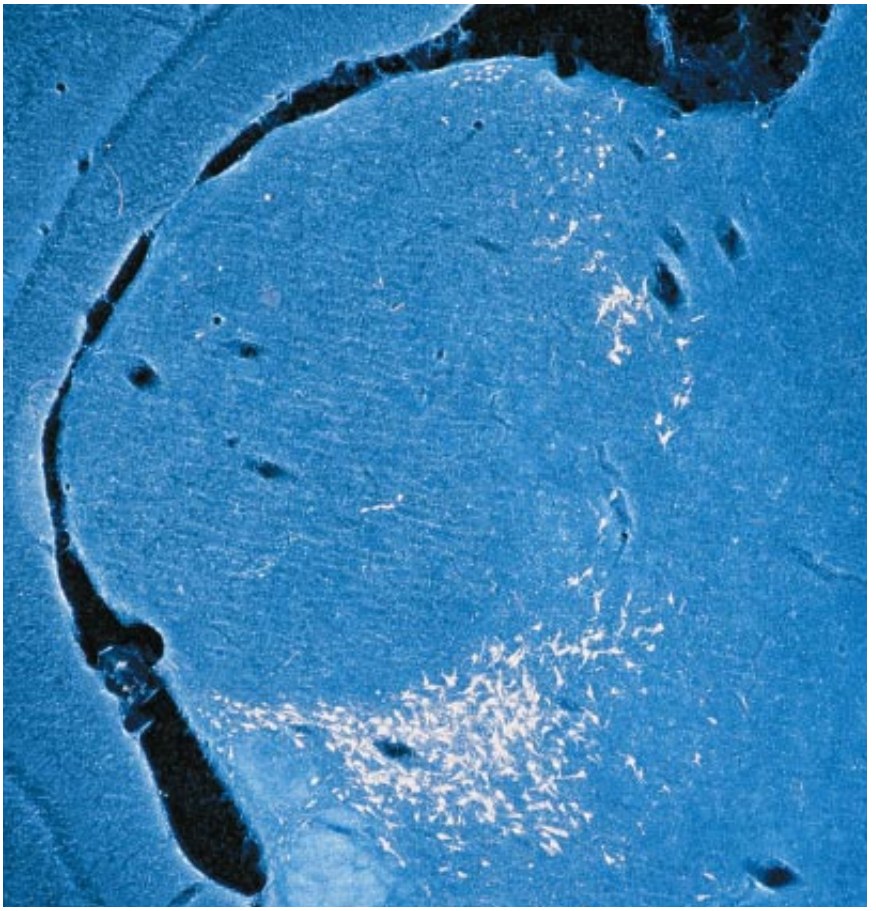

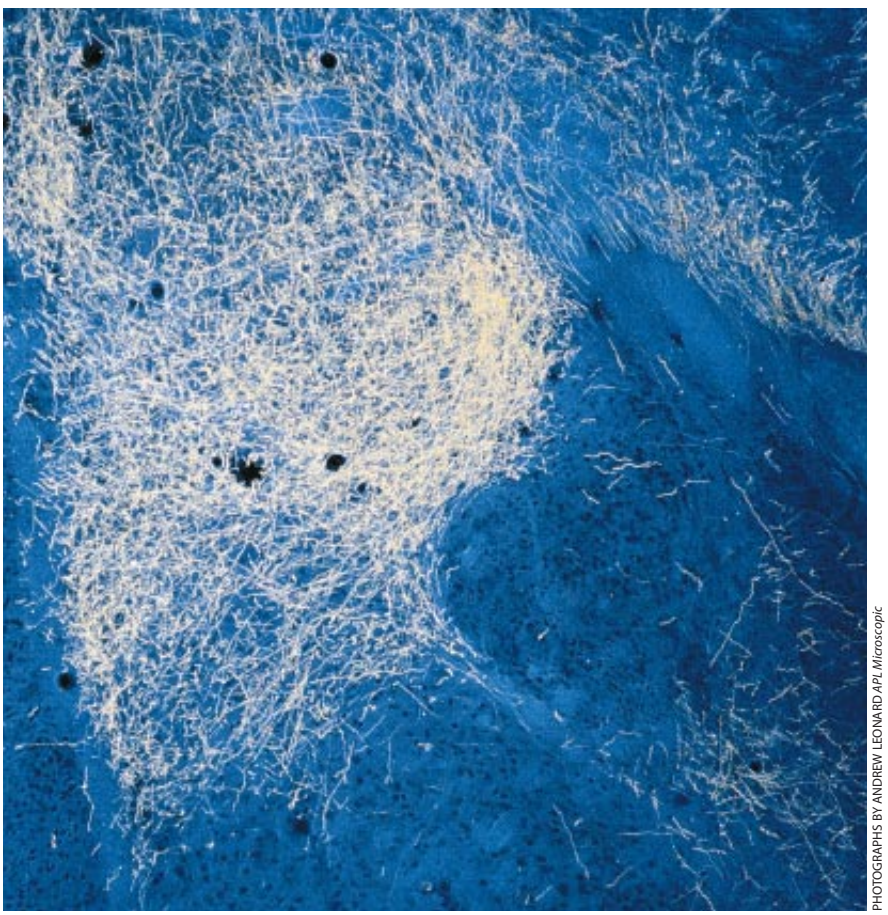

PHOTOGRAPHS BY ANDREW LEONARD *APL Microscopic*

ANATOMY OF EMOTION includes several regions of the brain. Shown here in the rat (*above*), parts of the amygdala, the thalamus and the cortex interact to create memories about fearful experiences associated, in this case, with sound. Recent work has located precise areas where fear is learned and remembered: certain parts of the thalamus (*light pink at top right*) communicate with areas in the amygdala (*light yellow at bottom right*) that process the fear-causing sound stimuli. Because these neural mechanisms are thought to be similar in humans, the study of emotional memory in rodents may illuminate aspects of fear disorders in people.

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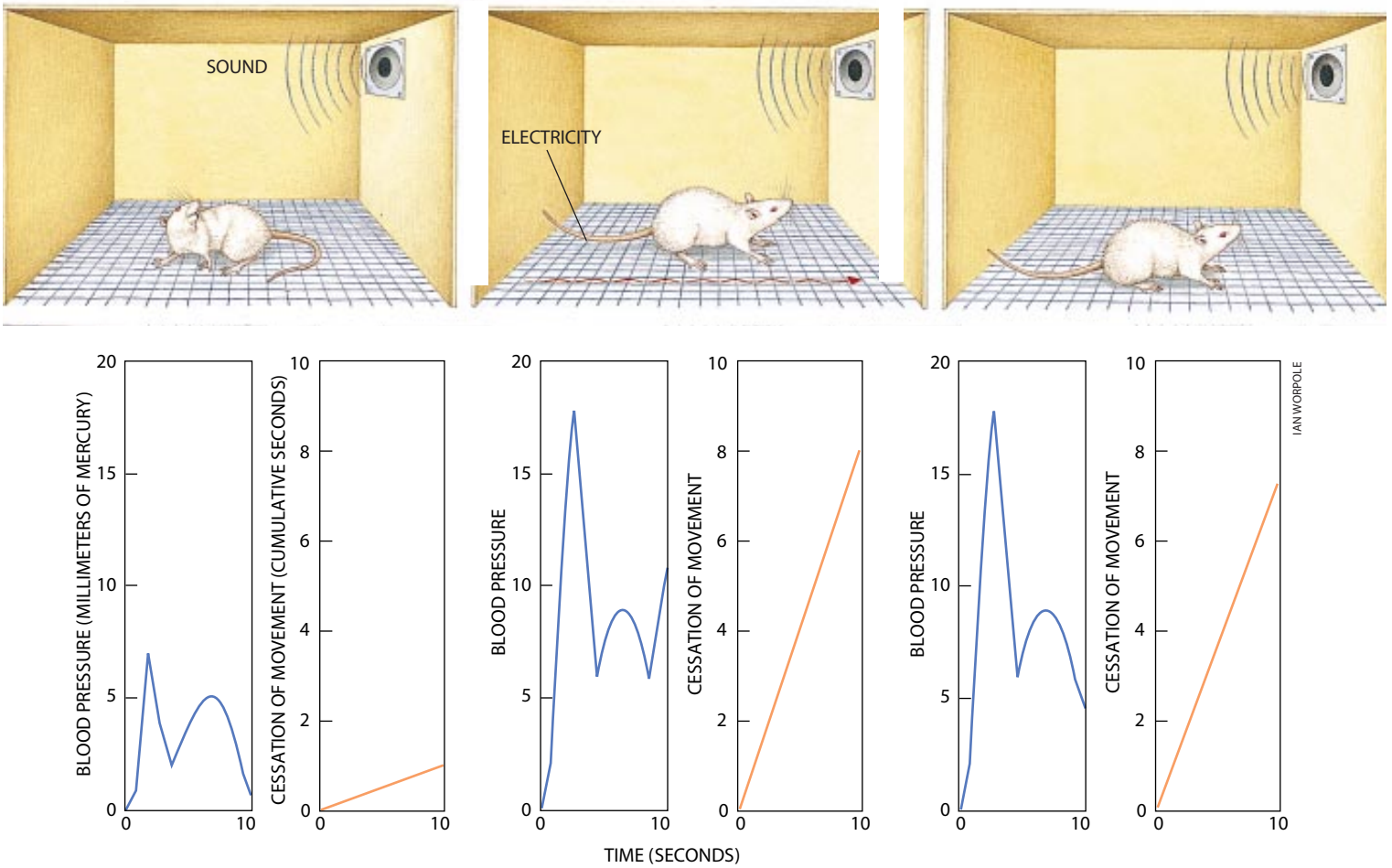

CLASSICAL FEAR CONDITIONING can be brought about by pairing a sound and a mild electric shock to the foot of a rat. In one set of experiments, the rat hears a sound (*left*), which has little effect on the animal's blood pressure or patterns of movement. Next, the rat hears the same sound, coupled with a foot shock (*center*). After several such pairings, the rat's blood pressure rises at the same time that the animal holds still for an extended period when it hears the sound. The rat has been fear-conditioned (*right*): sound alone achieves the same physiological changes as did sound and shock together.

cessfully treated. This resurrection demonstrates that the emotional memory underlying the phobia was rendered dormant rather than erased by treatment.

Fear and Emotional Memory

Fear conditioning has proved an ideal starting point for studies of emotional memory for several reasons. First, it occurs in nearly every animal group in which it has been examined: fruit flies, snails, birds, lizards, fish, rabbits, rats, monkeys and people. Although no one claims that the mechanisms are precisely the same in all these creatures, it seems clear from studies to date that the pathways are very similar in mammals and possibly in all vertebrates. We therefore are confident in believing that many of the findings in animals apply to humans. In addition, the kinds of stimuli most commonly used in this type of conditioning are not signals that rats—or humans, for that matter—encounter in their daily lives. The novelty and irrelevance of these lights and sounds help to ensure that the animals have not already developed strong emotional reactions to them. So researchers are clearly observing learning and memory at work. At the same time, such cues do not require complicated cognitive processing from the brain. Consequently, the stimuli permit us to study emotional mechanisms relatively directly. Finally, our extensive knowledge of the neural pathways involved in processing acoustic and visual information serves as an excellent starting point for examining the neurological foundations of fear elicited by such stimuli.

My work has focused on the cerebral roots of learning fear, specifically fear that has been induced in the rat by associating sounds with foot shock. As do most other investigators in the field, I assume that fear conditioning occurs because the shock modifies the way in which neurons in certain important regions of the brain interpret the sound stimulus. These critical neurons are thought to be located in the neural pathway through which the sound elicits the conditioned response.

During the past 10 years, researchers in my laboratory, as well as in others, have identified major components of this system. Our study began at Cornell University Medical College, where I worked several years ago, when my colleagues and I asked a simple question: Is the auditory cortex required for auditory fear conditioning?

In the auditory pathway, as in other sensory systems, the cortex is the highest level of processing; it is the culmination of a sequence of neural steps that starts with the peripheral sensory receptors, located, in this case, in the ear. If lesions in (or surgical removal of) parts of the auditory cortex interfered with

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ROBERTO OSTI

fear conditioning, we could conclude that the region is indeed necessary for this activity. We could also deduce that the next step in the conditioning pathway would be an output from the auditory cortex. But our lesion experiments in rats confirmed what a series of other studies had already suggested: the auditory cortex is not needed in order to learn many things about simple acoustic stimuli.

We then went on to make lesions in the auditory thalamus and the auditory midbrain, sites lying immediately below the auditory cortex. Both these areas process auditory signals: the midbrain provides the major input to the thalamus; the thalamus supplies the major input to the cortex. Lesions in both regions completely eliminated the rat's susceptibility to conditioning. This discovery suggested that a sound stimulus is transmitted through the auditory system to the level of the auditory thalamus but that it does not have to reach the cortex for fear conditioning to occur.

This possibility was somewhat puzzling. We knew that the primary nerve fibers that carry signals from the auditory thalamus extend to the auditory cortex. So David A. Ruggiero, Donald J. Reis and I looked again and found that, in fact, cells in some regions of the auditory thalamus also give rise to fibers that reach several subcortical locations. Could these neural projections be the connections through which the stimulus elicits the response we identify with fear? We tested this hypothesis by making lesions in each one of the subcortical regions with which these fibers connect. The damage had an effect in only one area: the amygdala.

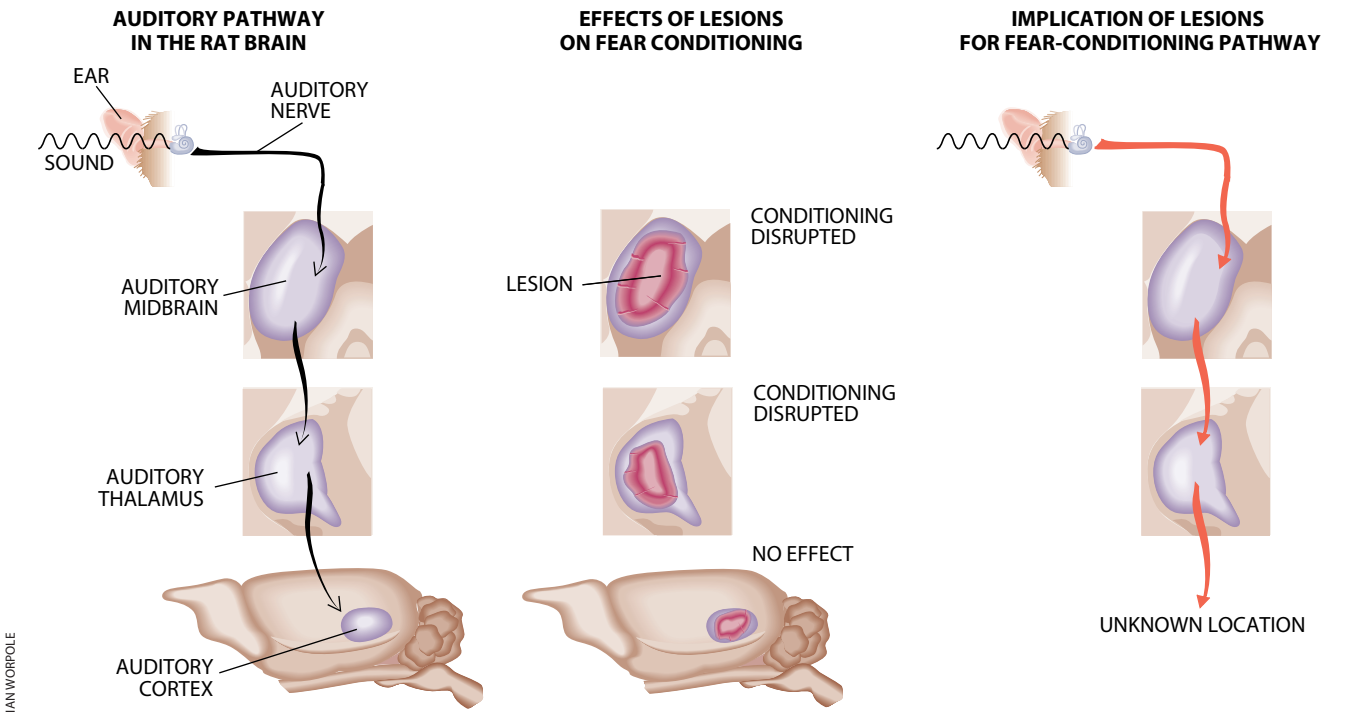
Filling in the Picture

That observation suddenly created a place for our findings in an already accepted picture of emotional processing. For a long time, the amygdala has been considered an important brain region in various forms of emotional behavior. In 1979 Bruce S. Kapp and his colleagues at the University of Vermont reported that lesions in the amygdala's central nucleus interfered with a rabbit's conditioned heart rate response once the animal had been given a shock paired with a sound. The central nucleus connects with areas in the brain stem involved in the control of heart rate, respiration and vasodilation. Kapp's work suggested that the central nucleus was a crucial part of the system through which autonomic conditioned responses are expressed.

In a similar vein, we found that lesions of this nucleus prevented a rat's blood pressure from rising and limited its ability to freeze in the presence of a fear-causing stimulus. We also demonstrated, in turn, that lesions of areas to which the central nucleus connects eliminated one or the other of the two responses. Michael Davis and his associates at Yale University determined that lesions of the central nucleus, as well as lesions of another brain stem area to which the central nucleus projects, diminished yet another conditioned response: the increased startle reaction that occurs when an animal is afraid.

The findings from various laboratories studying different species and measuring fear in different ways all implicated the central nucleus as a pivotal component of fear-conditioning circuitry. It provides connections to the various brain stem areas involved in the control of a spectrum of responses.

Despite our deeper understanding of this site in the amygdala, many details of the pathway remained hidden. Does



IAN WORPOLE

BRAIN LESIONS have been crucial to pinpointing the sites involved in experiencing and learning about fear. When a sound is processed by the rat brain, it follows a pathway from ear to midbrain to thalamus to cortex (*left*). Lesions can be made in various sites in the auditory pathway to determine which areas are necessary for fear conditioning (*center*). Only damage to the cortex does not disrupt the fear response, which suggests that some other areas of the brain receive the output of the thalamus and are involved in establishing memories about experiences that stimulate fear (*right*).

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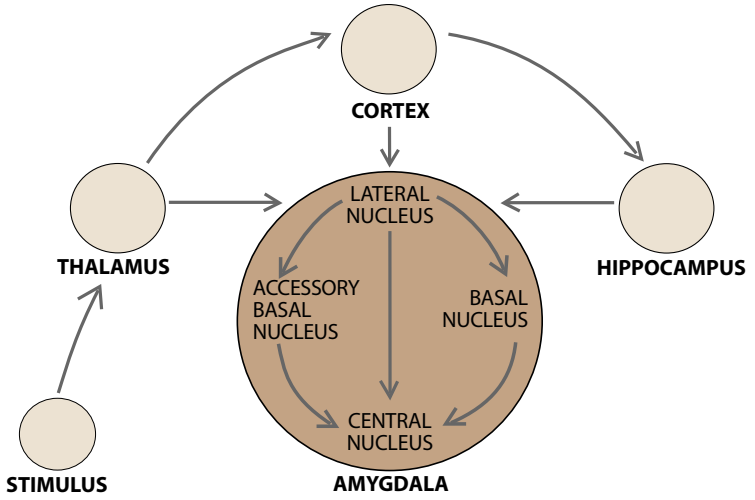
Structure of the Amygdala

The amygdala plays an important role in emotional behavior. Experiments in rodents have elucidated the structures of various regions of the amygdala and their role in learning about and remembering fear. The lateral nucleus receives inputs from sensory regions of the brain and transmits these signals to the basal, the accessory basal and the central nuclei. The central nucleus connects to the brain stem, bringing about physiological changes. *—J.E.LeD.*



sound, for example, reach the central nucleus directly from the auditory thalamus? We found that it does not. The central nucleus receives projections from thalamic areas next to, but not in, the auditory part of the thalamus. Indeed, an entirely different area of the amygdala, the lateral nucleus, receives inputs from the auditory thalamus. Lesions of the lateral nucleus prevented fear conditioning. Because this site gets information directly from the sensory system, we have come to think of it as the sensory interface of the amygdala in fear conditioning. In contrast, the central nucleus appears to be the interface with the systems that control responses.

Mapping the Mechanism

These findings seemed to place us on the threshold of being able to map the entire stimulus response pathway. But we still did not know how information received by the lateral nucleus arrived at the central nucleus. Earlier studies had suggested that the lateral nucleus projects directly to the central nucleus, but the connections were fairly sparse. Working with monkeys, David Amaral and Asla Pitkanen of the Salk Institute for Biological Studies in San Diego demonstrated that the lateral nucleus extends directly to an adjacent site, called the basal or basolateral nucleus, which, in turn, projects to the central nucleus.

Collaborating with Lisa Stefanacci and other members of the Salk team, Claudia R. Farb and C. Genevieve Go in my laboratory at New York University found the same connections in the rat. We then showed that these connections form synaptic contacts—in other words, they communicate directly, neuron to neuron. Such contacts indicate that information reaching the lateral nucleus can influence the central nucleus via the basolateral nucleus. The lateral nucleus can also influence the central nucleus by way of the accessory basal or basomedial nucleus. Clearly, ample opportunities exist for the lateral nucleus to communicate with the central nucleus once a stimulus has been received.

The emotional significance of such a stimulus is determined not only by the sound itself but by the environment in which it occurs. Rats must therefore learn not only that a sound or visual cue is dangerous, but under what conditions it is so. Russell G. Phillips and I examined the response of rats to the chamber, or context, in which they had been conditioned. We found that lesions of the amygdala interfered with the animals' response to both the tone and the chamber. But lesions of the hippocampus—a region of the brain involved in declarative memory—interfered only with response to the chamber, not the tone. (Declarative memory involves explicit, consciously accessible information, as well as spatial memory.) At about the same time, Michael S. Fanselow and Jeansok J. Kim of the University of California at Los Angeles discovered that hippocampal lesions made after fear conditioning had taken place also prevented the expression of responses to the surroundings.

These findings were consistent with the generally accepted view that the hippocampus plays an important role in processing complex information, such as details about the spatial environment where activity is taking place. Phillips and I also demonstrated that the subiculum, a region of the hippocampus that projects to other areas of the brain, communicated with the lateral nucleus of the amygdala. This connection suggests that contextual information may acquire emotional significance in the same way that other events do—via transmission to the lateral nucleus.

Although our experiments had identified a subcortical sensory pathway that gave rise to fear conditioning, we did not dismiss the importance of the cortex. The interaction of subcortical and cortical mechanisms in emotion remains a hotly debated topic. Some researchers believe cognition is a vital precursor to emotional experience; others think that cognition—which is presumably a cortical function—is necessary to initiate emotion or that emotional processing is a type of cognitive processing. Still others question whether cognition is necessary for emotional processing.

It became apparent to us that the auditory cortex is involved in, though not crucial to, establishing the fear response, at least when simple auditory stimuli are applied. Norman M. Weinberger and his colleagues at the University of California at Irvine have performed elegant studies showing that neurons in the auditory cortex undergo specific physiological changes in their reaction to sounds as a result of conditioning. This finding indicates that the cortex is establishing its own record of the event.

Experiments by Lizabeth M. Romanski in my laboratory have determined that in the absence of the auditory cortex, rats can learn to respond fearfully to a single tone. If, however, projections from the thalamus to the amygdala are removed, projections from the thalamus to the cortex and then to the amygdala

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are sufficient. Romanski went on to establish that the lateral nucleus can receive input from both the thalamus and the cortex. Her work in the rat complements earlier research in primates.

Once we had a clear understanding of the mechanism through which fear conditioning is learned, we attempted to find out how emotional memories are established and stored on a molecular level. Farb and I showed that the excitatory amino acid transmitter glutamate is present in the thalamic cells that reach the lateral nucleus. Together with Chiye J. Aoki, we showed that it is also present at synapses in the lateral nucleus. Because glutamate transmission is implicated in memory formation, we seemed to be on the right track.

Long-Term Potentiation

Glutamate has been observed in a process called long-term potentiation, or LTP, that has emerged as a model for the creation of memories. This process, which is most frequently studied in the hippocampus, involves a change in the efficiency of synaptic transmission along a neural pathway—in other words, signals travel more readily along this pathway once LTP has taken place. The mechanism seems to involve glutamate transmission and a class of postsynaptic excitatory amino acid receptors known as NMDA receptors.

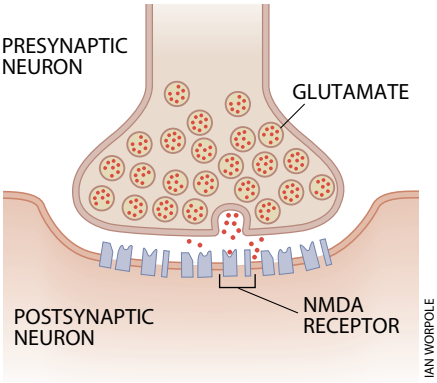
Various studies have found LTP in the fear-conditioning pathway. Marie-Christine Clugnet and I noted that LTP could be induced in the thalamo-amygdala pathway. Thomas H. Brown and Paul Chapman and their colleagues at Yale discovered LTP in a cortical projection to the amygdala. Other researchers, including Davis and Fanselow, have been able to block fear conditioning by blocking NMDA receptors in the amygdala. And Michael T. Rogan in my laboratory found that the processing of sounds by the thalamo-amygdala pathway is amplified after LTP has been induced. The fact that LTP can be demonstrated in a conditioning pathway offers new hope for understanding how LTP might relate to emotional memory.

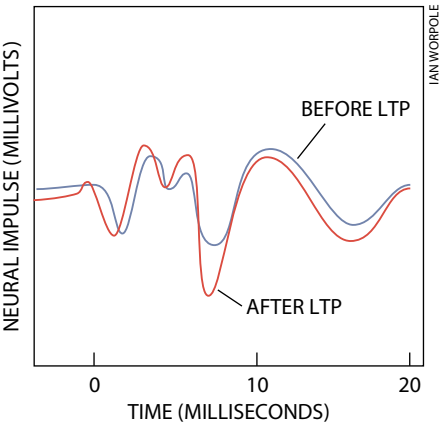
In addition, recent studies by Fabio Bordi, also in my laboratory, have suggested hypotheses about what could be going on in the neurons of the lateral nucleus during learning. Bordi monitored the electrical state of individual neurons in this area when a rat was listening to the sound and receiving the shock. He and Romanski found that essentially every cell responding to the auditory stimuli also responded to the shock. The basic ingredient of conditioning is thus present in the lateral nucleus.

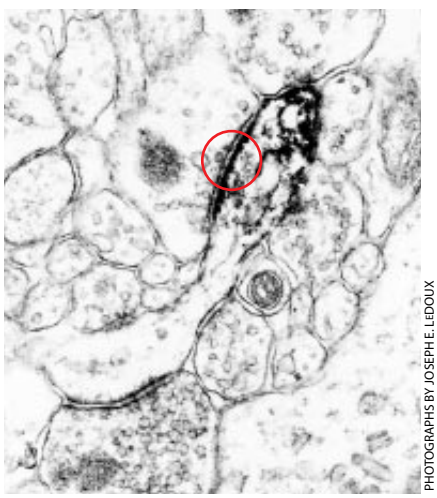
Bordi was able to divide the acoustically stimulated cells into two classes: habituating and consistently responsive. Habituating cells eventually stopped responding to the repeated sound, suggesting that they might serve to detect any sound that was unusual or different. They could permit the amygdala to ignore a stimulus once it became familiar. Sound and shock pairing at these cells might reduce habituation, thereby allowing the cells to respond to, rather than ignore, significant stimuli.

The consistently responsive cells had high-intensity thresholds: only loud sounds could activate them. That finding is interesting because of the role loudness plays in judging distance. Nearby sources of sound are presumably more dangerous than those that are far away. Sound coupled with shock might act on these cells to lower their threshold, increasing the cells' sensitivity to the same stimulus. Consistently responsive cells were also broadly tuned. The joining of a sound and a shock could make the cells responsive to a narrower range of frequencies, or it could shift the tuning toward the frequency of the stimulus. In fact, Weinberger has recently shown that cells in the auditory system do alter their tuning to approximate the conditioned stimulus. Bordi and I have detected this effect in lateral nucleus cells as well.

The apparent permanence of these memories raises an important clinical question: Can emotional learning be eliminated, and, if not, how can it be toned down? As noted earlier, it is actually quite difficult to get rid of emotional memories, and at best we can hope







MEMORY FORMATION has been linked to the establishment of long-term potentiation, or LTP. In this model of memory the neurotransmitter glutamate and its receptors, called NMDA receptors (*top*), bring about strengthened neural transmission. Once LTP is established, the same neural signals produce larger responses (*top, middle*). Emotional memories may also involve LTP in the amygdala. Glutamate (*red circle in top photograph*) and NMDA receptors (*red circle in bottom photograph*) have been found in the region of the amygdala where fear conditioning takes place.

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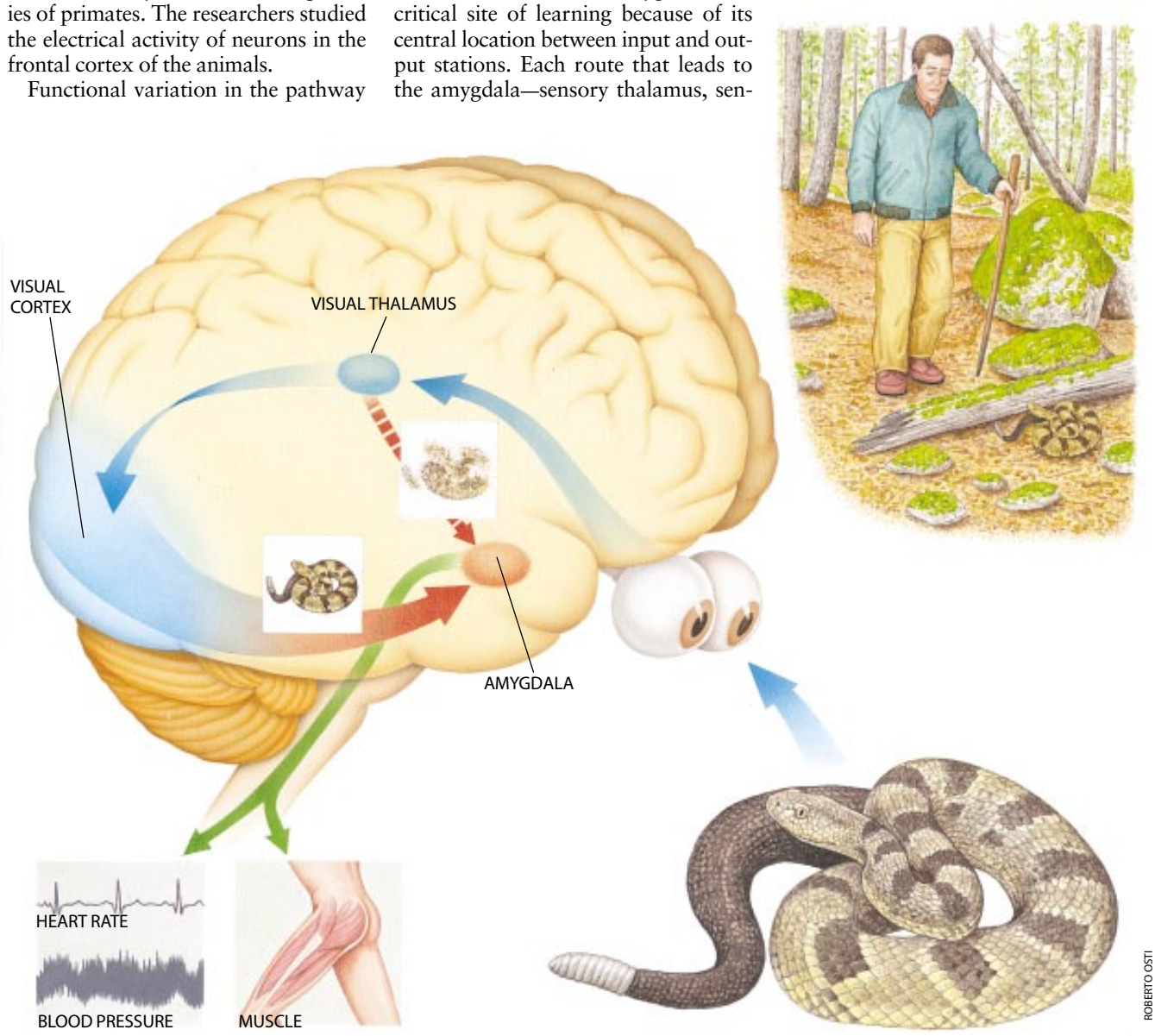
only to keep them under wraps. Studies by Maria A. Morgan in my laboratory have begun to illuminate how the brain regulates emotional expressions. Morgan has shown that when part of the prefrontal cortex is damaged, emotional memory is very hard to extinguish. This discovery indicates that the prefrontal areas—possibly by way of the amygdala—normally control expression of emotional memory and prevent emotional responses once they are no longer useful. A similar conclusion was proposed by Edmund T. Rolls and his colleagues at the University of Oxford during studies of primates. The researchers studied the electrical activity of neurons in the frontal cortex of the animals.

Functional variation in the pathway between this region of the cortex and the amygdala may make it more difficult for some people to change their emotional behavior. Davis and his colleagues have found that blocking NMDA receptors in the amygdala interferes with extinction. Those results hint that extinction is an active learning process. At the same time, such learning could be situated in connections between the prefrontal cortex and the amygdala. More experiments should disclose the answer.

Placing a basic emotional memory process in the amygdalic pathway yields obvious benefits. The amygdala is a critical site of learning because of its central location between input and output stations. Each route that leads to the amygdala—sensory thalamus, sensory cortex and hippocampus—delivers unique information to the organ. Pathways originating in the sensory thalamus provide only a crude perception of the external world, but because they involve only one neural link, they are quite fast. In contrast, pathways from the cortex offer detailed and accurate representations, allowing us to recognize an object by sight or sound. But these pathways, which run from the thalamus to the sensory cortex to the amygdala, involve several neural links. And each link in the chain adds time.



ROBERTO OSTI

CORTICAL AND SUBCORTICAL PATHWAYS in the brain—generalized from our knowledge of the auditory system—may bring about a fearful response to a snake on a hiker's path. Visual stimuli are first processed by the thalamus, which passes rough, almost archetypal, information directly to the amygdala (*red*). This quick transmission allows the brain to start to respond to the possible danger (*green*). Meanwhile the visual cortex also receives information from the thalamus and, with more perceptual sophistication and more time, determines that there is a snake on the path (*blue*). This information is relayed to the amygdala, causing heart rate and blood pressure to increase and muscles to contract. If, however, the cortex had determined that the object was not a snake, the message to the amygdala would quell the fear response.

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Conserving time may be the reason there are two routes—one cortical and one subcortical—for emotional learning. Animals, and humans, need a quick-and-dirty reaction mechanism. The thalamus activates the amygdala at about the same time as it activates the cortex. The arrangement may enable emotional responses to begin in the amygdala before we completely recognize what it is we are reacting to or what we are feeling.

The thalamic pathway may be particularly useful in situations requiring a rapid response. Failing to respond to danger is more costly than responding inappropriately to a benign stimulus. For instance, the sound of rustling leaves is enough to alert us when we are walking in the woods without our having first to identify what is causing the sound. Similarly, the sight of a slender curved shape lying flat on the path ahead of us is sufficient to elicit defensive fear responses. We do not need to go through a detailed analysis of whether or not what we are seeing is a snake. Nor do we need to think about the fact that snakes are reptiles and that their skins can be used to make belts and boots. All these details are irrelevant and, in fact, detrimental to an efficient, speedy and potentially lifesaving reaction. The brain simply needs to be able to store primitive cues and detect them. Later, coordination of this basic information with the cortex permits verification (yes, this is a snake) or brings the response (screaming, sprinting) to a stop.

Storing Emotional Memory

Although the amygdala stores primitive information, we should not consider it the only learning center. The establishment of memories is a function of the entire network, not just of one component. The amygdala is certainly crucial, but we must not lose sight of the fact that its functions exist only by virtue of the system to which it belongs.

Memory is generally thought to be the process by which we bring back to mind some earlier conscious experience. The original learning and the remembering, in this case, are both conscious events. Workers have determined that declarative memory is mediated by the hippocampus and the cortex. But removal of the hippocampus has little effect on fear conditioning—except conditioning to context.

In contrast, emotional learning that comes about through fear conditioning is not declarative learning. Rather it is mediated by a different system, which in all likelihood operates independently of our conscious awareness. Emotional information may be stored within declarative memory, but it is kept there as a cold declarative fact. For example, if a person is injured in an automobile accident in which the horn gets stuck in the on position, he or she may later have a reaction when hearing the blare of car horns. The person may remember the details of the accident, such as where and when it occurred, who else was involved and how awful it was. These are declarative memories that are dependent on the hippocampus. The individual may also become tense, anxious and depressed, as the emotional memory is reactivated through the amygdalic system. The declarative system has stored the emotional content of the experience, but it has done so as a fact.

Emotional and declarative memories are stored and retrieved in parallel, and their activities are joined seamlessly in our conscious experience. That does not mean that we have direct conscious access to our emotional memory; it means instead that we have access to the consequences—such as the way we behave, the way our bodies feel. These consequences combine with current declarative memory to form a new declarative memory. Emotion is not just unconscious memory: it exerts a powerful influence on declarative memory and other thought processes. As James L. McGaugh and his colleagues at the University of California at Irvine have convincingly shown, the amygdala plays an essential part in modulating the storage and strength of memories.

The distinction between declarative memory and emotional memory is an important one. W. J. Jacobs of the University of British Columbia and Lynn Nadel of the University of Arizona have argued that we are unable to remember traumatic events that take place early in life because the hippocampus has not yet matured to the point of forming consciously accessible memories. The emotional memory system, which may develop earlier, clearly forms and stores its unconscious memories of these events.

Emotional and declarative memories are joined seamlessly in our conscious experience. That does not mean we have direct conscious access to our emotional memory.

And for this reason, the trauma may affect mental and behavioral functions in later life, albeit through processes that remain inaccessible to consciousness.

Because pairing a tone and a shock can bring about conditioned responses in animals throughout the phyla, it is clear that fear conditioning cannot be dependent on consciousness. Fruit flies and snails, for example, are not creatures known for their conscious mental processes. My way of interpreting this phenomenon is to consider fear a subjective state of awareness brought about when brain systems react to danger. Only if the organism possesses a sufficiently advanced neural mechanism does conscious fear accompany bodily response. This is not to say that only humans experience fear but, rather, that consciousness is a prerequisite to subjective emotional states.

Thus, emotions or feelings are conscious products of unconscious processes. It is crucial to remember that the subjective experiences we call feelings are not the primary business of the system that generates them. Emotional experiences are the result of triggering systems of behavioral adaptation that have been preserved by evolution. Subjective experience of any variety is challenging turf for scientists. We have, however, gone a long way toward understanding the neural system that underlies fear responses, and this same system may in fact give rise to subjective feelings of fear. If so, studies of the neural control of emotional responses may hold the key to understanding subjective emotion as well. SA

Further Reading

THE AMYGDALA: NEUROBIOLOGICAL ASPECTS OF EMOTION, MEMORY AND MENTAL DYSFUNCTION. Edited by John P. Aggleton. Wiley-Liss, 1992.

BRAIN MECHANISMS OF EMOTION AND EMOTIONAL LEARNING. J. E. LeDoux in *Current Opinion in Neurobiology.* Vol. 2, No. 2, pages 191–197; April 1992.

THE ROLE OF THE AMYGDALA IN FEAR AND ANXIETY. M. Davis in *Annual Review of Neuroscience,* Vol. 15, pages 353–375; 1992.

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The Neurobiology of Fear

Researchers are teasing apart the neurochemical processes that give rise to different fears in monkeys. The results may lead to new ways to treat anxiety in humans

by Ned H. Kalin

The Author

NED H. KALIN, a clinician and researcher, is professor of psychiatry and psychology and chairman of the department of psychiatry at the University of Wisconsin–Madison Medical School. He is also a scientist at the Wisconsin Regional Primate Research Center and the Harlow Primate Laboratory at the university. He earned his B.S. degree in 1972 from Pennsylvania State University and his M.D. in 1976 from Jefferson Medical College in Philadelphia. Before joining his current departments, he completed a residency program in psychiatry at Wisconsin and a postdoctoral fellowship in clinical neuropharmacology at the National Institute of Mental Health.

Wild monkey displays cooing—a typical fear behavior.

Over the years, most people acquire a repertoire of skills for coping with a range of frightening situations. They will attempt to placate a vexed teacher or boss and will shout and run when chased by a mugger. Some individuals, though, become overwhelmed in circumstances others would consider only minimally stressful: fear of ridicule might cause them to shake uncontrollably when called on to speak in a group, or terror of strangers might lead them to hide at home, unable to work or shop for groceries. Why do certain people fall prey to excessive fear?

At the University of Wisconsin at Madison, my colleague Steven E. Shelton and I are addressing this problem by identifying specific brain processes that regulate fear and its associated behaviors. Despite the availability of noninvasive imaging techniques, such information is still extremely difficult to obtain in humans. Hence, we have turned our attention to another primate, the rhesus monkey (*Macaca mulatta*). These animals undergo many of the same physiological and psychological developmental stages that humans do, but in a more compressed time span. As we gain more insight into the nature and operation of neural circuits that modulate fear in monkeys, it should be possible to pinpoint the brain processes that cause inordinate anxiety in people and to devise new therapies to counteract it.

Effective interventions would be particularly beneficial if they were applied at an early age. Growing evidence suggests overly fearful youngsters are at high risk for later emotional distress. Jerome Kagan and his colleagues at Harvard University have shown, for example, that a child who is profoundly shy at the age of two years is more likely than a less inhibited child to suffer from anxiety and depression later in life.

This is not to say these ailments are inevitable. But it is easy to see how excessive fear could contribute to a lifetime of emotional struggle. Consider a child who is deeply afraid of other children and is therefore taunted by them at school. That youngster might begin to feel unlikable and, in turn, to withdraw further. With time the growing child could become mired in a vicious circle leading to isolation, low self-esteem, underachievement and the anxiety and depression noted by Kagan.

There are indications that unusually fearful children might

NED H. KALIN

RHESUS MONKEY REGISTERS ALARM (*right*) as another monkey approaches her baby. The mother's fear is evident in her "threat" face: the open mouth and piercing stare serve to intimidate would-be attackers and intruders.

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also be prone to physical illness. Many youngsters who become severely inhibited in unfamiliar situations chronically overproduce stress hormones, including the adrenal product cortisol. In times of threat, these hormones are critical. They ensure that muscles have the energy needed for "fight or flight." But some evidence indicates long-term elevations of stress hormones may contribute to gastric ulcers and cardiovascular disease.

Further, through unknown mechanisms, fearful children and their families are more likely than others to suffer from allergic disorders. Finally, in rodents and nonhuman primates, persistent elevation of cortisol has been shown to increase the vulnerability of neurons in the hippocampus to damage by other substances; this brain region is involved in memory, motivation and emotion. Human neurons probably are affected in a similar manner, although direct evidence is awaited.

When we began our studies about 10 years ago, Shelton and I knew we would first have to find cues that elicit fear and identify behaviors that reflect different types of anxiety. With such information in hand, we could proceed to determine the age at which monkeys begin to match defensive behaviors selectively to specific cues. By also determining the parts of the brain that reach maturity during the same time span, we could gain clues to the regions that underlie the regulation of fear and fear-related behavior.

The experiments were carried out at the Wisconsin Regional Primate Research Center and the Harlow Primate Laboratory, both at the University of Wisconsin. We discerned varied behaviors by exposing monkeys between six and 12 months old to three related situ-

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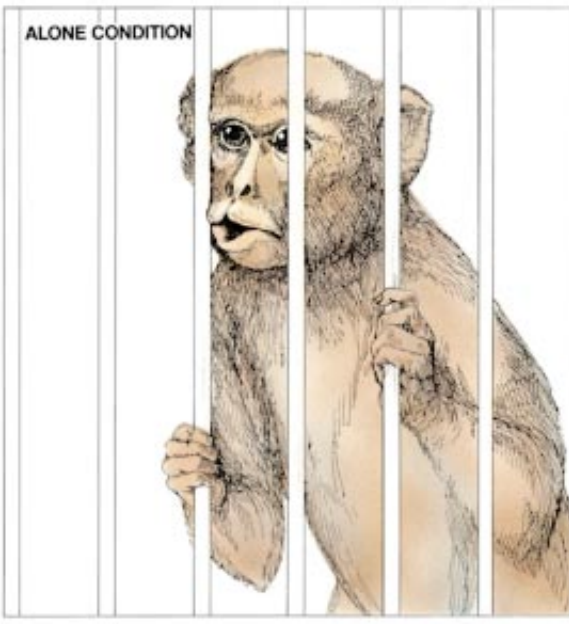

THREE EXPERIMENTAL CONDITIONS elicit distinct fear-related behaviors in rhesus monkeys older than about two months. When isolated in a cage (*left*), youngsters become quite active and emit "coo" sounds to attract their mothers. If a human appears but avoids eye contact (*center*), the monkeys try to evade discovery, such as by staying completely still (freezing) or hiding behind their food bin. If the intruder stares at the animals (*right*), they become aggressive.

ations. In the alone condition, an animal was separated from its mother and left by itself in a cage for 10 minutes. In the no-eye-contact condition, a person stood motionless outside the cage and avoided looking at the solitary infant. In the stare condition, a person was again present and motionless but, assuming a neutral expression, peered directly at the animal. These conditions are no more frightening than those primates encounter frequently in the wild or those human infants encounter every time they are left at a day-care center.

Three Typical Fear Behaviors

In the alone condition, most monkeys became very active and emitted frequent "coo" calls. These fairly melodious sounds are made with pursed lips. They start at a low pitch, become higher and then fall. More than 30 years ago Harry F. Harlow, then at Wisconsin, deduced that when an infant monkey is separated from its mother, its primary goal is affiliative—that is, it yearns to regain the closeness and sense of security provided by nearness to the parent. Moving about and cooing help to draw the mother's attention.

In contrast, in the more frightening no-eye-contact situation, the monkeys reduced their activity greatly and sometimes "froze," remaining completely still for prolonged periods. When an infant spots a possible predator, its goal shifts from attracting the mother to becoming inconspicuous. Inhibiting motion and freezing—common responses in many species—reduce the likelihood of attack.

If the infant perceives that it has been detected, its aim shifts again, to warding off an attack. And so the stare condition evoked a third set of responses. The monkeys made several hostile gestures, among them "barking" (forcing air from the abdomen through the vocal cords to emit a growllike sound), staring back, producing so-called threat faces [*see illustration on preceding page*], baring their teeth and shaking the cage. Sometimes the animals mixed the threatening displays with submissive ones, such as fear grimaces, which look something like wary grins, or grinding of the teeth. In this condition, too, cooing increased over the amount heard when the animals were alone. (As will be seen, we have recently come to think the cooing displayed in the stare condition may serve a somewhat different function than it does in the alone situation.)

Monkeys, by the way, are not unique in becoming aroused by stares and in using them reciprocally to intimidate predators. Animals as diverse as crabs, lizards and birds all perceive staring as a threat. Some fishes and insects have evolved protective spots that resemble eyes; these spots either avert attacks completely or redirect them to nonvital parts of the body. In India, field-workers wear face masks behind their heads to discourage tigers from pouncing at their backs. Studies of humans show that we, too, are sensitive to direct gazes: brain activity increases when we are stared at, and people who are anxious or depressed tend to avoid direct eye contact.

Having identified three constellations of defensive behaviors, we set about determining when infant monkeys first begin to apply them effectively. Several lines of work led us to surmise that the ability to make such choices emerges sometime around an infant's two-month birthday. For instance, rhesus mothers generally permit children to venture off with their peers at that time, presumably because the adults are now confident that the infants can protect themselves reasonably well. We also knew that by about 10 weeks of age infant monkeys respond with different emotions to specific expressions on the faces of other monkeys—a sign that at least some of the innate wiring or learned skills needed to discriminate threatening cues are in place.

To establish the critical period of de-

TYPICAL BEHAVIORS induced by the alone, no-eye-contact and stare conditions in the laboratory—such as cooing (*left*), freezing (*center*) and hostile display of the teeth (*right*)—are also seen in frightened infants and adults living in the wild. In this case, the setting is Cayo Santiago, an island off the mainland of Puerto Rico.

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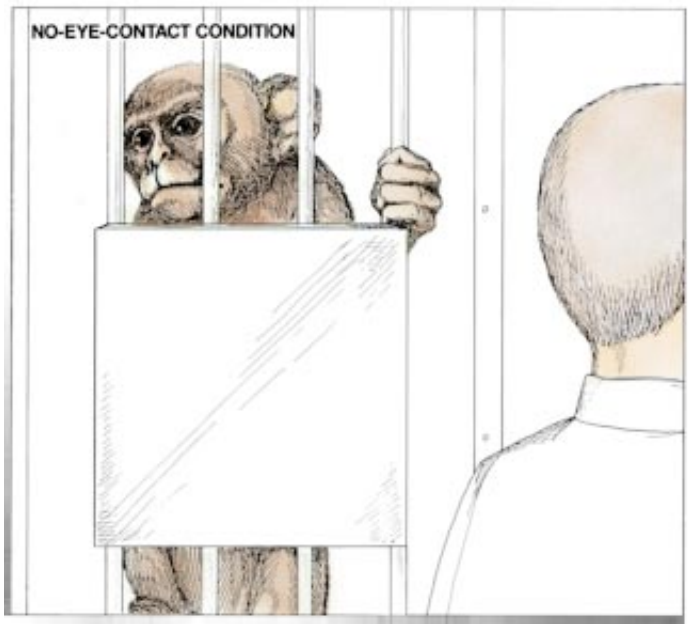

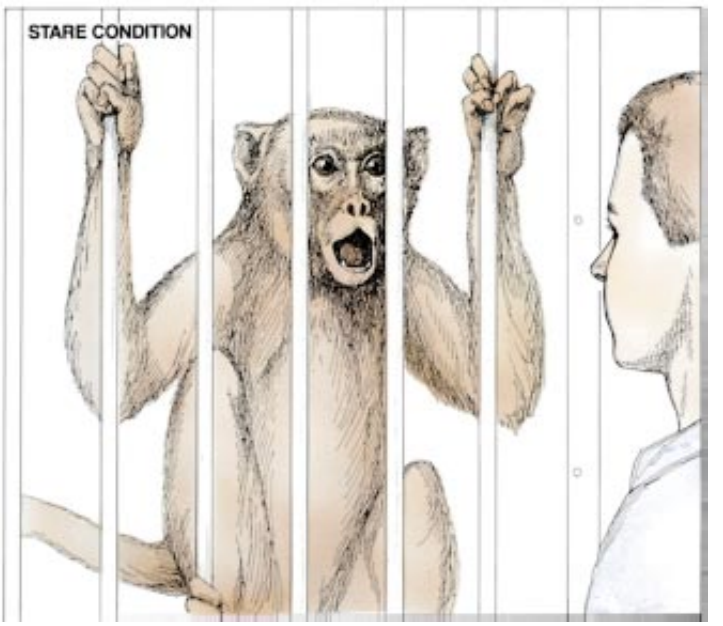

velopment, we examined four groups of monkeys ranging in age from a few days to 12 weeks old. We separated the babies from their mothers and let them acclimate to an unfamiliar cage. Then we exposed them to the alone, no-eye-contact and stare conditions. All sessions were videotaped for analysis.

We found that infants in the youngest group (newborns to two-week-olds) engaged in defensive behaviors. But they lacked some motor coordination and seemed to act randomly, as if they were oblivious to the presence or gaze of the human intruder. Babies in our two intermediate-age groups had good motor control, but their actions seemed unrelated to the test condition. This finding meant motor control was not the prime determinant of selective responding.

Only animals in our oldest group (nine- to 12-week-olds) conducted themselves differently in each situation, and their reactions were both appropriate and identical to those of mature monkeys. Nine to 12 weeks, then, is the critical age for the appearance of a monkey's ability to adaptively modulate its defensive activity to meet changing demands.

Studies by other workers, who primarily examined rodents, suggested that three interconnected parts of the brain regulate fearfulness. We suspected that these regions become functionally mature during the nine- to 12-week period and thus give rise to the selective reactivity we observed. One of these regions is the prefrontal cortex, which takes up much of the outer and side areas of the cerebral cortex in the frontal lobe [*see top illustration on next page*]. A cognitive and emotional area, the prefrontal cortex is thought to participate in the interpretation of sensory stimuli and is probably a site where the potential for danger is assessed.

The second region is the amygdala, a part of a primitive area in the brain called the limbic system (which includes the hippocampus). The limbic system in general and the amygdala in particular have been implicated in generating fear.

The final region is the hypothalamus. Located at the base of the brain, it is a

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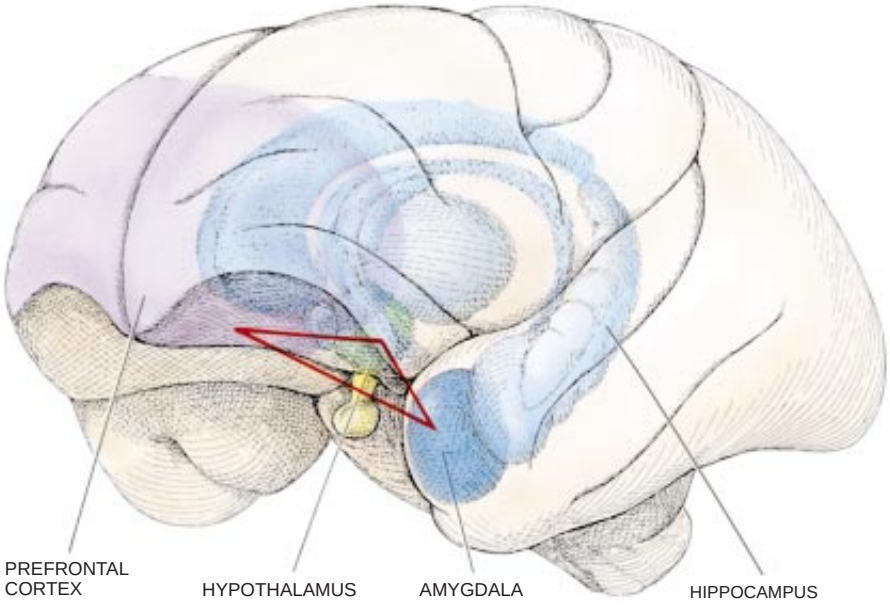

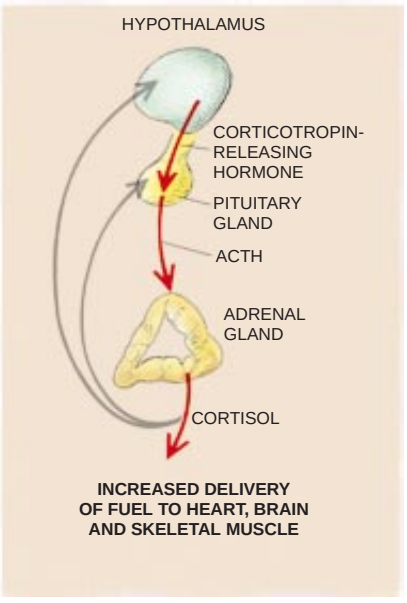

CAROL DONNER

THREE BRAIN REGIONS that are interconnected by neural pathways (*shown schematically by red lines*) are critically important in regulating fear-related behaviors. The prefrontal cortex (*purple*) participates in assessing danger. The amygdala (*dark blue*) is a major constituent of the emotion-producing limbic system (*light blue*). And the hypothalamus (*green*), in response to signals from the prefrontal cortex, amygdala and hippocampus, directs the release of hormones (*red arrows in box*) that support motor responses to perceived threats. (Gray arrows represent inhibitory activity by cortisol.)

constituent of what is called the hypothalamic-pituitary-adrenal system. In response to stress signals from elsewhere in the brain, such as the limbic system and other cortical regions, the hypothalamus secretes corticotropin-releasing hormone. This small protein spurs the pituitary gland, located just below the brain, to secrete adrenocorticotropic hormone (ACTH), which prods the adrenal gland to release cortisol, which prepares the body to defend itself.

In neuroanatomic data collected in other laboratories, we found support for our suspicion that maturation of these brain regions underlies selective responding in the nine- to 12-week period. For instance, during this time the formation of synapses (contact points between neurons) has been shown to reach its peak in the prefrontal cortex and the limbic

NED H. KALIN

INFANT (*left*) has strayed a short distance from its mother (*center*) and is producing a rudimentary threat face in an attempt to keep a photographer (the author) at bay. Rhesus monkeys become adept at matching their behavior to the severity and type of a threat when they are between nine and 12 weeks old, probably because certain neuronal pathways in three regions of the brain—the prefrontal cortex, amygdala and hypothalamus—reach functional maturity during this same period.

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system (including the amygdala), as well as in the motor and visual cortices and other sensory areas. Patricia S. Goldman-Rakic of Yale University has also established that as the prefrontal cortex matures in rhesus monkeys, the ability to guide behavior based on experience emerges. This skill is necessary if one is to contend successfully with danger.

Maturation of the prefrontal cortex likewise seems important for enabling humans to distinguish among threatening cues. Harry T. Chugani and his coworkers at the University of California at Los Angeles have shown that activity in the prefrontal cortex increases when human offspring are seven to 12 months of age. During this span—which appears to be analogous to the time when monkeys begin to respond selectively to fear—children begin to display marked fear of strangers. They also become adept at what is called social referencing; they regulate their level of fear based on interpreting the expressions they observe on a parent's face.

But what of the hypothalamus, the third brain region we assumed could participate in regulating fear-related behavior? Published research did not tell us much about its development or about the development of the complete hypothalamic-pituitary-adrenal system in monkeys. Our own investigations, however, revealed that the full system matures in parallel with that of the prefrontal cortex and the limbic system.

In these studies, we used the pituitary hormone ACTH as a marker of the system's function. We again examined four groups of infants aged a few days to 12 weeks. From each subject, we measured ACTH levels in blood drawn while the youngster was with its mother. This reading provided a baseline. We also measured ACTH levels in blood samples obtained 20 minutes after the infant was separated from its parent. Hormonal levels rose in all four age groups during separation, but they jumped profoundly only in the oldest (nine- to 12-week-old) monkeys.

The relatively weak response in the younger animals, particularly in those under two weeks old, is consistent with findings in rat pups, whose stress hormone response is also blunted during the first two weeks of life. The development of the rodent and primate stress hormone system may well be delayed during early life to protect young neurons from the potentially damaging effects of cortisol.

Assured that the hypothalamic-pituitary-adrenal system becomes functionally mature by nine to 12 weeks, we pressed the inquiry forward to determine whether levels of cortisol and ACTH might partly account for individual differences in defensive behavior. We were also curious to know whether the responses of the infants resembled those of their mothers; a correspondence would indicate that further analyses of mothers and their infants could help reveal the relative contributions of inheritance and learning to fearfulness. We mainly examined the propensity for freezing, which we had earlier found was a stable trait in our subjects.

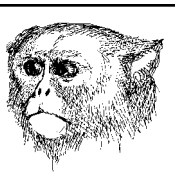
Maturing of the Fear Response

In one set of studies, we measured baseline levels of cortisol in monkeys four months to a year old and then observed how much time the youngsters froze in the no-eye-contact condition. Monkeys that started off with relatively low levels of cortisol froze for shorter periods than did their counterparts with higher cortisol levels—a pattern we also noted in separate studies of adult females. In other studies, we observed that as youngsters pass through their first year of life, they become progressively like their mothers hormonally and behaviorally. By the time infants are about five months old, their stress-induced rises in ACTH levels parallel those of the mothers. And by the time they are a year old, the duration of freezing in the no-eye-contact condition also corresponds to that of the mother.

Strikingly, some of these results echoed those obtained in humans. Extremely inhibited children often have parents who suffer from anxiety. Moreover, Kagan and his colleagues have found that basal cortisol levels are predictive of such children's reaction to a frightening situation. They measured cortisol concentrations in saliva of youngsters at home (where they are presumably most relaxed) and then observed the children confronting an unfamiliar situation in the laboratory; high basal cortisol levels were associated with greater inhibition in the strange setting.

These similarities between humans and monkeys again imply that monkeys are reasonable models of human emotional reactivity. The link between basal cortisol levels and duration of freezing or inhibition suggests as well that levels of stress hormones influence how appropriately animals and people behave in the face of fear. (This effect may partly be mediated by the hippocampus, where the concentration of cortisol receptors is high.) And the likeness of hormonal and behavioral responses in mothers and infants implies that genetic inheritance might predispose some individuals to extreme fearfulness, although we cannot rule out the contribution of experience.

No one can yet say to what extent the activity of the hypothalamic-pituitary-adrenal system controls, and is controlled by, other brain regions that reg-



	COOING	FREEZING	BARKING
MORPHINE (OPIATE)	DECREASES	NO EFFECT	NO EFFECT
NALOXONE (OPIATE BLOCKER)	INCREASES	NO EFFECT	NO EFFECT
DIAZEPAM (BENZODIAZEPINE)	NO EFFECT	DECREASES	DECREASES

CAROL DONNER

EFFECTS ON COOING, FREEZING AND BARKING were evaluated some years ago for three drugs that act on neurons responsive to opiates (*top two rows*) or to benzodiazepines (*bottom row*). The results implied that opiate-sensitive pathways in the brain control affiliative behaviors (those that restore closeness to the mother, as cooing often does), whereas benzodiazepine-sensitive pathways control responses to immediate threats (such as freezing and barking). Newer evidence generally supports this conclusion but adds some complexity to the picture.

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ulate the choice of defensive behavior. We have, however, begun to identify distinct neurochemical circuits, or systems, in the brain that affect different behaviors. The two systems we have studied most intensely seemed at first to have quite separate functions. But more recent work implies that the controls on defensive behavior are rather more complicated than the original analyses implied.

We gathered our initial data three years ago by treating six- to 12-month-old monkeys with two different classes of neuroactive chemicals—opiates (morphinelike substances) and benzodiazepines (chemicals that include the antianxiety drug diazepam, or Valium). We chose to look at opiates and benzodiazepines because neurons that release or take up those chemicals are abundant in the prefrontal cortex, the amygdala and the hypothalamus. The opiates are known to have natural, or endogenous, counterparts, called endorphins and enkephalins, that serve as neurotransmitters; after the endogenous chemicals are released by certain neurons, they bind to receptor molecules on other nerve cells and thereby increase or decrease nerve cell activity. Receptors for benzodiazepines have been identified, but investigators are still trying to isolate endogenous benzodiazepinelike molecules.

PHOTOGRAPHS BY NED H. KALIN

RELAXED MOTHER (*left*) barely reacts to the presence of the camera-wielding author, whereas a more sensitive mother becomes frightened (*right*), as evinced by her "fear gri-

Selective Drug Effects

Once again, our subjects were exposed to the alone, no-eye-contact and stare conditions. We delivered the drugs before the infants were separated from their mothers and then recorded the animals' behavior. Morphine decreased the amount of cooing normally displayed in the alone and stare conditions. Conversely, cooing was increased by naloxone, a compound that binds to opiate receptors but blocks the activity of morphine and endogenous opiates. Yet morphine and naloxone had no influence on the frequency of stare-induced barking and other hostile behaviors, nor did they influence duration of freezing in the no-eye-contact situation. We concluded that opiate-using neural pathways primarily regulate affiliative behaviors (such as those induced by distress over separation from the mother), but those pathways seem to have little power over responses to direct threats.

The benzodiazepine we studied—diazepam—produced a contrary picture. The drug had no impact on cooing, but it markedly reduced freezing, barking and other hostile gestures. Thus, benzodiazepine-using pathways seemed primarily to influence responses to direct threats but to have little power over affiliative behavior.

We still think the opiate and benzodiazepine pathways basically serve these separate functions. Nevertheless, the simple model we initially envisioned grew more interesting as we investigated two additional drugs: a benzodiazepine called alprazolam (Xanax) and a compound called beta-carboline, which binds to benzodiazepine receptors but elevates anxiety and typically produces effects opposite to those of diazepam and its relatives.

When we administered alprazolam in doses that lower anxiety enough to decrease freezing, this substance, like diazepam, minimized hostility in the threatening, stare condition. And beta-carboline enhanced hostility. No surprises here. Yet, unlike diazepam, these drugs modulated cooing, which we had considered to be an affiliative (opiate-controlled), not a threat-related (benzodiazepine-controlled), behavior. Moreover, both these compounds decreased cooing. We cannot explain the similarity of effect, but we have some ideas about why drugs that act on benzodiazepine receptors might influence cooing.

It may be that, contrary to our early view, benzodiazepine pathways can in fact regulate affiliative behavior. We favor a second interpretation, however. Cooing displayed in the stare condition may not solely reflect an affiliative need (a desire for mother's comfort); at times, it may also be an urgent, threat-induced plea for immediate help. One behavior, then, might serve two different functions and be controlled by different neurochemical pathways. (This conclusion was strengthened for me recently, when I tried to photograph a rhesus infant that had become separated from its mother in the wild—where we are now initiating additional studies. Its persistent, intense coos attracted the mother, along with a pack of protectors. The strategy worked: I retreated rapidly.)

More generally, our chemical studies lead us to suspect that the opiate- and benzodiazepine-sensitive circuits both operate during stress; the relative degree of activity changes with the characteristics of a worrisome situation. As the contribution of each pathway is altered, so, too, are the behaviors that appear.

Exactly how neurons in the opiate and benzodiazepine pathways function and how they might cooperate are unclear. But one plausible scenario goes like this: When a young monkey is separated from its mother, opiate-releasing and, consequently, opiate-sensitive neurons become inhibited. Such inhibition gives rise to yearning for the mother and a generalized sense of vulnerability. This

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mace." The author hopes explorations of the neural bases for such differences in monkeys will facilitate development of new therapies for excessively anxious human beings.

reduction of activity in opiate-sensitive pathways enables motor systems in the brain to produce cooing. When a potential predator appears, neurons that secrete endogenous benzodiazepines become suppressed to some degree. This change, in turn, leads to elevated anxiety and the appearance of behaviors and hormonal responses that accompany fear. As the sense of alarm grows, motor areas prepare for fight or flight. The benzodiazepine system may also influence the opiate system, thereby altering cooing during threatening situations.

We are now refining our model of brain function by testing other compounds that bind to opiate and benzodiazepine receptors. We are also examining behavioral responses to substances, such as the neurotransmitter serotonin, that act on other receptors. (Serotonin receptors occur in many brain regions that participate in the expression of fear.) And we are studying the activities of substances that directly control stress hormone production, including corticotropin-releasing hormone, which is found throughout the brain, not solely in the hypothalamus.

In collaboration with Richard J. Davidson, here at Wisconsin, Shelton and I have recently identified at least one brain region where the benzodiazepine system exerts its effects. Davidson had shown that the prefrontal cortex of the right hemisphere is unusually active in extremely inhibited children. We therefore wondered whether we would see the same asymmetry in frightened monkeys and whether drugs that reduced fear-related behavior in the animals would dampen right frontal activity.

This time we used mild restraint as a stress. As we anticipated, neuronal firing rose more in the right frontal cortex than in the left. Moreover, when we delivered diazepam in doses we knew lowered hostility, the drug returned the restraint-induced electrical activity to normal. In other words, the benzodiazepine system influences defensive behavior at least in part by acting in the right prefrontal cortex.

These findings have therapeutic implications. If human and monkey brains do operate similarly, our data would suggest that benzodiazepines might be most helpful in those adults and children who exhibit elevated electrical activity in the right prefrontal cortex. Because of the potential for side effects, many clinicians are cautious about delivering antianxiety medications to children over a long time. But administration of such drugs during critical periods of brain development might prove sufficient to alter the course of later development. It is also conceivable that behavioral training could teach extremely inhibited youngsters to regulate benzodiazepine-sensitive systems without having to be medicated. Alternatively, by screening compounds that are helpful in monkeys, investigators might discover new drugs that are quite safe for children. As the workings of other fear-modulating neurochemical systems in the brain are elucidated, similar strategies could be applied to manage those circuits.

Our discovery of cues that elicit three distinct sets of fear-related behaviors in rhesus monkeys has thus enabled us to gain insight into the development and regulation of defensive strategies in these animals. We propose that the opiate and benzodiazepine pathways in the prefrontal cortex, the amygdala and the hypothalamus play a major part in determining which strategies are chosen. And we are currently attempting to learn more about the ways in which these and other neural circuits cooperate with one another. We have therefore laid the groundwork for deciphering the relative contributions of various brain systems to inordinate fear in humans. We can envision a time when treatments will be tailored to normalizing the specific signaling pathways that are disrupted in a particular child, thereby sparing that youngster enormous unhappiness later in life. SA

Further Reading

LOVE IN INFANT MONKEYS. Harry F. Harlow in *Scientific American,* Vol. 200, No. 6, pages 68–74; June 1959.

THE ETHOLOGY OF PREDATION. Eberhard Curio. Springer-Verlag, 1976.

STRESS AND COPING IN EARLY DEVELOPMENT. Jerome Kagan in *Stress, Coping, and Development in Children.* Edited by N. Garmezy and M. Rutter. McGraw-Hill, 1983.

DEFENSIVE BEHAVIORS IN INFANT RHESUS MONKEYS: ENVIRONMENTAL CUES AND NEUROCHEMICAL REGULATION. Ned H. Kalin and Steven E. Shelton in *Science,* Vol. 243, pages 1718–1721; March 31, 1989.

STRESS IN THE WILD. Robert M. Sapolsky in *Scientific American,* Vol. 262, No. 1; January 1990.

DEFENSIVE BEHAVIORS IN INFANT RHESUS MONKEYS: ONTOGENY AND CONTEXT-DEPENDENT SELECTIVE EXPRESSION. N. H. Kalin, S. E. Shelton and L. K. Takahashi in *Child Development,* Vol. 62, No. 5, pages 1175–1183; October 1991.

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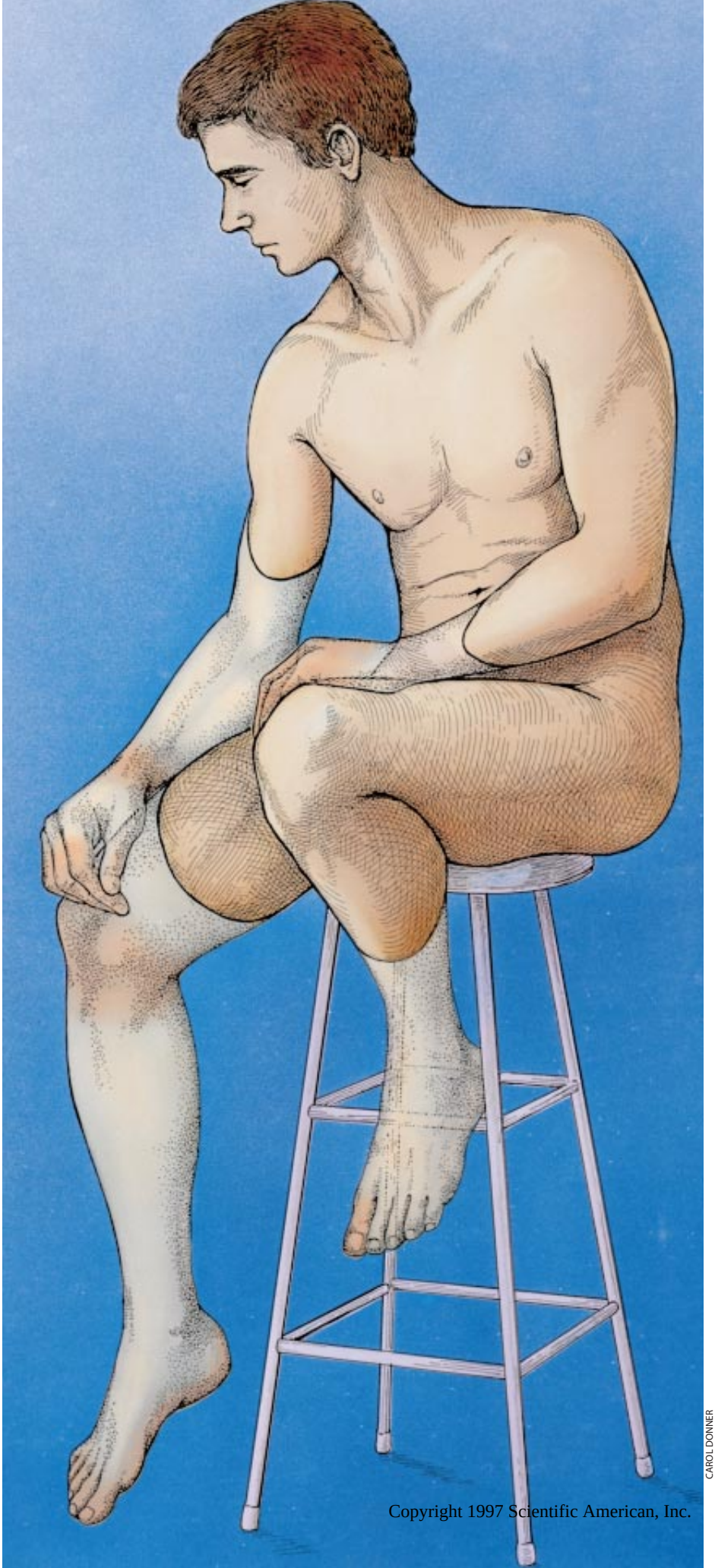
Phantom Limbs



CAROL DONNER

The Author

RONALD MELZACK is E. P. Taylor Professor of Psychology at McGill University and research director of the Pain Clinic at Montreal General Hospital. His work on the neurophysiology of pain spans almost four decades. After obtaining his Ph.D. in psychology at McGill in 1954 and taking up fellowships in the U.S. and abroad, he joined the faculty of the Massachusetts Institute of Technology in 1959. There he and Patrick D. Wall began discussions that led to the publication in 1965 of their now famous "gate control" theory of pain. Melzack joined the McGill faculty in 1963. This is his fourth article for *Scientific American*.

Stimulation elsewhere in the body can sometimes be felt in a phantom limb.

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People who have lost an arm or a leg often perceive the limb as though it were still there. Treating the pain of these ghostly appendages remains difficult

by Ronald Melzack

In 1866 S. Weir Mitchell, the foremost American neurologist of his time, published his first account of phantom limbs, not in a scientific journal but in the *Atlantic Monthly,* as an anonymously written short story. In his tale, "The Case of George Dedlow," the protagonist loses an arm to amputation during the Civil War. Later, he awakens in the hospital after, unbeknownst to him, both his legs have also been amputated.

"[I was] suddenly aware of a sharp cramp in my left leg. I tried to get at it…with my single arm, but, finding myself too weak, hailed an attendant. 'Just rub my left calf,…if you please.' "

" 'Calf?…You ain't got none, pardner. It's took off.' "

Some historians have speculated that Mitchell chose to publish in the *Atlantic* as a way of testing the reaction of his peers to the concept of phantom limbs. He feared they would not believe amputated arms and legs could be felt after the limbs were gone.

In fact, the phenomenon of phantom limbs is common. So is the occurrence of terrible pain in these invisible appendages. Yet neither the cause of phantoms nor the associated suffering is well understood. My colleagues and I have recently proposed explanations that are leading to fresh research into treatments for the often intractable pain. The concepts also raise questions about basic assumptions of contemporary psychology and neuroscience.

The most extraordinary feature of phantoms is their reality to the amputee. Their vivid sensory qualities and precise location in space—especially at first—make the limbs seem so lifelike that a patient may try to step off a bed onto a phantom foot or lift a cup with a phantom hand. The phantom, in fact, may seem more substantial than an actual limb, particularly if it hurts.

In most cases, a phantom arm hangs straight down at the side when the person sits or stands, but it moves in perfect coordination with other limbs during walking; that is, it behaves like a normal limb. Similarly, a phantom leg bends as it should when its owner sits; it stretches out when the individual lies down; and it becomes upright during standing.

Sometimes, however, the amputee is sure the limb is stuck in some unusual position. One man felt that his phantom arm extended straight out from the shoulder, at a right angle to the body. He therefore turned sideways whenever he passed through doorways, to avoid hitting the wall. Another man, whose phantom arm was bent behind him, slept only on his abdomen or on his side because the phantom got in the way when he tried to rest on his back.

The eerie reality of phantoms is often reinforced by sensations that mimic feelings in the limb before amputation. For example, a person may feel a painful ulcer or bunion that had been on a foot or even a tight ring that had been on a finger. Such individuals are not merely recollecting sensations but are feeling them with the full intensity and detail of an ongoing experience. The reality of the phantom is also enhanced by wearing an artificial arm or leg; the phantom usually fills the prosthesis as a hand fits a glove.

The sense of reality is also strengthened by the wide range of sensations a phantom limb can have. Pressure, warmth, cold and many different kinds of pain are common. A phantom can feel wet (as when an artificial foot is seen stepping into a puddle). Or it can itch, which can be extremely distressing, although scratching the apparent site of discomfort can sometimes actually relieve the annoyance. The person may also feel as if the limb is being tickled or is sweaty or prickly.

Naturally, of all the sensations in phantom limbs, pain, which as many as 70 percent of amputees suffer, is the most frightening and disturbing. It is often described as burning, cramping or shooting and can vary from being occasional and mild to continuous and severe. It usually starts shortly after amputation but sometimes appears weeks, months or years later. A typical complaint is that a hand is clenched, fingers bent over the thumb and digging into the palm, so that the whole hand is tired and achy. In the leg the discomfort may be felt as a cramp in the calf. Many patients report that their toes feel as if they are being seared by a red-hot poker.

The existence of phantoms in people born without a limb suggests that the neural networks for perceiving the body are built into the brain.

A final striking feature of phantoms, which reinforces the reality still further, is that they are experienced as a part of oneself. That is, patients perceive them as integral parts of the body. A phantom foot is described not only as real but as unquestionably belonging to the person. Even when the foot is felt to be dangling in the air several inches beneath the stump and unconnected to the leg, it is still experienced as part of one's body, and it moves appropriately with the other limbs and with the torso.

Amputation is not essential for the occurrence of a phantom. In some acci-

TYPICAL EXAMPLES of phantom limbs reported by patients are combined in this human figure. Some parts of the phantom are felt especially vividly (*highlighted areas in transparent limbs*). The phantom limb is perceived as perfectly real to the patient, who describes it as being in various positions and often reports feeling pain in it.

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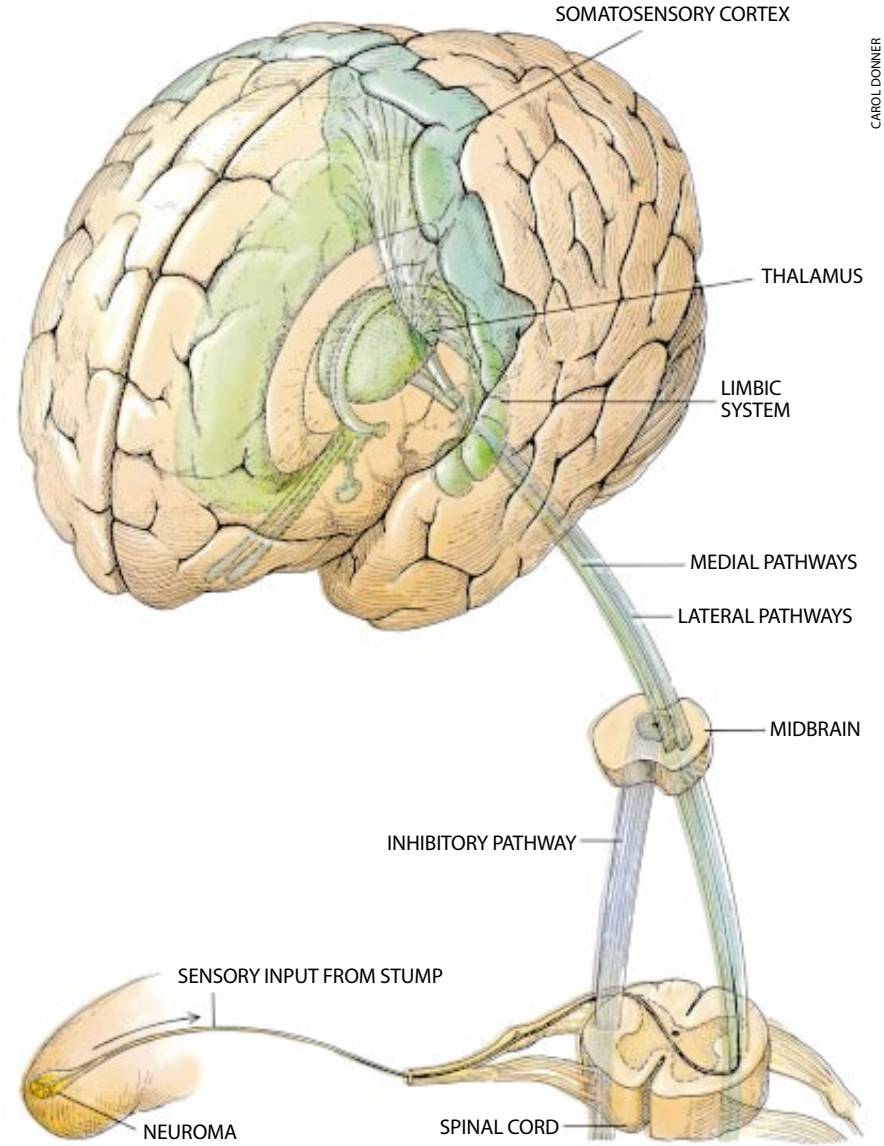

CAROL DONNER

PATHWAYS OF SIGNALS from the body to the brain are shown. After the loss of a limb, nerve cells in the denervated areas of the spinal cord and brain fire spontaneously at high levels and with abnormal bursting patterns.

dents, particularly when a rider is thrown off a motorcycle and hits the pavement, the shoulder is wrenched forward so that all the nerves from the arm are ripped from the spinal cord, a condition known as a brachial plexus avulsion. The resulting phantom occupies the now useless true arm and is usually coordinated with it. But if the victim's eyes are closed, the phantom will remain in its original position when the real arm is moved by someone else. Although the flesh-and-blood arm is incapable of responding to stimulation, the phantom version is usually extremely painful. Regrettably, even surgical removal of the true arm has no effect on the phantom or on the pain.

Similarly, paraplegics—persons who have had a complete break of the spinal cord and therefore have no feeling in, or control over, their body below the break—often have phantom legs and other body parts, including genitals. Immediately after an accident, the phantom may be dissociated from the real body. For instance, a person may feel as if the legs are raised over the chest or head even when he or she can see that they are stretched out on the road. Later, though, phantoms move in coordination with the body, at least when the person's eyes are open. Some paraplegics complain that their legs make continuous cycling movements, producing painful fatigue, even though a patient's actual legs are lying immobile on the bed. Phantoms are also reported by patients whose spinal cords are anesthetized, such as by a spinal block during labor.

The oldest explanation for phantom limbs and their associated pain is that the remaining nerves in the stump, which grow at the cut end into nodules called neuromas, continue to generate impulses. The impulses flow up through the spinal cord and parts of the thalamus (which is a central way station in the brain) to the somatosensory areas of the cortex. These cortical areas are the presumed centers for sensation in classical concepts of the nervous system.

On the basis of this explanation, treatments for pain have attempted to halt the transmission of impulses at every level of the somatosensory projection system. The nerves from the stump have been cut, usually just above the neuroma or at the roots—small bundles of fibers that arise when the sensory nerves divide into smaller branches, just before they enter the spinal cord. Pathways within the spinal cord have been cut as well, and the areas of the thalamus and cortex that ultimately receive sensory information from the limb have been removed.

Although these approaches may provide relief for months or even years, the pain usually returns. Moreover, none of these procedures abolish the phantom limb itself. Hence, neuroma activity cannot by itself account either for the phenomenon of the phantom limb or for the suffering.

A related hypothesis moves the source of phantom limbs from neuromas to the spinal cord, suggesting that phantoms arise from excessive, spontaneous firing of spinal cord neurons that have lost their normal sensory input from the body. The output of the cells is transmitted to the cortex, just as if the spinal neurons had received external stimulation. This proposal grew in part out of research done in the 1960s showing that after sensory nerves in the body are cut, neurons in the spinal cord spontaneously generate a high level of electrical impulses, often in an abnormal, bursting pattern.

Other observations indicate that this explanation is insufficient. Paraplegics who have suffered a complete break of the spinal cord high in the upper body sometimes feel severe pain in the legs and groin. Yet the spinal neurons that carry messages from those areas to the brain originate well below the level of the break, which means that any nerve impulses arising in those neurons would not traverse the break.

Some recent work has led to the proposal that phantom limbs can arise still

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higher in the central nervous system—in the brain itself. One hypothesis holds that phantoms are caused by changes in the flow of signals through the somatosensory circuit in the brain.

For example, Frederick A. Lenz, then at the University of Toronto, observed abnormally high levels of activity and a bursting pattern in cells of the thalamus in a paraplegic patient who had a full break of the spinal cord just below the neck but nonetheless suffered pain in the lower half of his body. The overactive cells, it turned out, also responded to touches the head and neck, even though the cells were in the area of the thalamus that normally responds only to stimulation of the body below the level of the cut. This finding suggested that neural inhibition was lifted on the flow of signals across existing but previously unused synapses in sensory neurons projecting to the thalamus from the head and neck.

Such changes in the somatosensory thalamus or cortex could help explain why certain feelings arise in limbs that no longer exist or can no longer transmit signals to the brain. Nevertheless, alterations in this system cannot by themselves account for phantoms and their pain. If this explanation were sufficient, removal of the affected parts of the somatosensory cortex or thalamus would solve both problems.

Clearly, the source of phantom limbs is more complex than any of these theories would suggest. No other hypotheses have been proposed, however. As an outgrowth of my interest in the brain mechanisms that give rise to pain, I have pondered the causes of phantoms and phantom-limb pain and studied patients with these problems for many years.

Self-Awareness Neuromatrix

My work and that of others have led me to conclude that, to a great extent, phantom limbs originate in the brain, as the work of Lenz would suggest. But much more of the cerebrum than the somatosensory system is involved.

Any explanation must account for the rich variety of sensations a person can feel, the intense reality of the phantom and the conviction that even free-floating phantoms belong to the self. I have proposed such a model. It has been well received, but it must, of course, be tested more fully before its value can be assessed completely. Meanwhile, though, it has already generated new ideas for research into stopping the pain that arises from phantom limbs.

In essence, I postulate that the brain contains a neuromatrix, or network of neurons, that, in addition to responding to sensory stimulation, continuously generates a characteristic pattern of impulses indicating that the body is intact and unequivocally one's own. I have called this pattern a neurosignature. If such a matrix operated in the absence of sensory inputs from the periphery of the body, it would create the impression of having a limb even after that limb has been removed.

To produce all the qualities I have described for phantoms, the matrix would have to be quite extensive, including at least three major neural circuits in the brain. One of them, of course, is the clas-

Phantom Seeing and Hearing

Phantom seeing and hearing, like phantom limbs, are also generated by the brain in the absence of sensory input. People whose vision has been impaired by cataracts or by the loss of a portion of the visual processing system in the brain sometimes report highly detailed visual experiences. This syndrome was first described in 1769, when the philosopher Charles Bonnet wrote an article on the remarkable visual experiences of his grandfather, Charles Lullin, who had lost most of his vision because of cataracts but was otherwise in good physical and psychological health. Since then, many mentally sound individuals have reported similarly vivid phantom visual experiences.

Phantom seeing often coexists with a limited amount of normal vision. The person experiencing the phantom has no difficulty in differentiating between the two kinds of vision. Phantom visual episodes appear suddenly and unexpectedly when the eyes are open. People usually describe the visual phantoms as seeming real despite the obvious impossibility of their existence. Common phantom images include people and large buildings. Rarer perceptions include miniature people and small animals. Phantom sights are not mere memories of earlier experiences; they often contain events, places or people that have never before been encountered.

First appearances of phantom images can be quite startling. A woman in one of our studies who had lost much of her vision because of retinal degeneration reported being shocked when she looked out a window and saw a tall building in what she knew to be a wooded field. Even though she realized that the building was a phantom, it seemed so real that she could count its steps and describe its other details. The building soon disappeared, only to return several hours later. The phantom vision continues to come and go unexpectedly, she explained to my student Geoffrey Schultz.

Phantom seeing occurs most among the elderly, presumably because vision tends to deteriorate with age. Some 15 percent of the people who lose all or part of their vision report phantom visual experiences. The proportion may be higher because some people avoid discussing phantom vision for fear of being labeled as psychologically disturbed.

Phantom sounds are also extremely common, although few people recognize them for what they are. People who lose their hearing commonly report noises in their heads. These noises, called tinnitus, are said to sound like whistling, clanging, screeching or the roaring of a train. They can be so loud and unpleasant that the victim needs help to cope with the distress they cause.

Some people with tinnitus report hearing "formed sounds," such as music or voices. A woman who had been a musician before losing her hearing says she "hears" piano concertos and sonatas. The impression is so real that at first she thought the sounds were coming from a neighbor's radio. The woman reports that she cannot turn off the music and that it often gets louder at night when she wants to go to sleep. Another woman, who had lost much of her sight and hearing, experienced both phantom sight and sound. In one instance, she described seeing a circus and hearing the music that accompanied the acts.

Phantom sights and sounds, like phantom limbs, occur when the brain loses its normal input from a sensory system. In the absence of input, cells in the central nervous system become more active. The brain's intrinsic mechanisms transform that neuronal activity into meaningful experiences. *—R.M.*

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sical sensory pathway passing through the thalamus to the somatosensory cortex. A second system must consist of the pathways leading through the reticular formation of the brain stem to the limbic system, which is critical for emotion and motivation. I include this circuit in part because I and others have noted that paraplegics who suffer a complete spinal break high in the upper body continue to experience themselves as still being in their old body, and they describe the feelings in the denervated areas with the same kinds of affective terms as they did before they were injured, such as "painful," "pleasurable" or "exhausting."

A final system consists of cortical regions important to recognition of the self and to the evaluation of sensory signals. A major part of this system is the parietal lobe, which in studies of brain-damaged patients has been shown to be essential to the sense of self.

Indeed, patients who have suffered a lesion of the parietal lobe in one hemisphere have been known to push one of their own legs out of a hospital bed because they were convinced it belonged to a stranger. Such behavior shows that the damaged area normally imparts a signal that says, "This is my body; it is a part of my self."

I believe that when sensory signals from the periphery or elsewhere reach the brain, they pass through each of these systems in parallel. As the signals are analyzed, information about them is shared among the three systems and converted into an integrated output, which is sent to other parts of the brain. Somewhere in the brain the output is transformed into a conscious perception, although no one knows exactly where the transformation that leads to awareness takes place.

As dynamic as this description may seem, the processing is probably still more dynamic than that. I further propose that as the matrix analyzes sensory information, it imprints its characteristic neurosignature on the output. Thus, the output carries information about sensory input as well as the assurance that the sensation is occurring in one's own body. The neurosignature may be likened to the basic theme of an orchestral piece. The collective sound changes when different instruments play their parts (the input), but the product is continually shaped by the underlying theme (the neurosignature), which provides the continuity for the work, even as the details of its rendition change.

Genetically Prewired Matrix

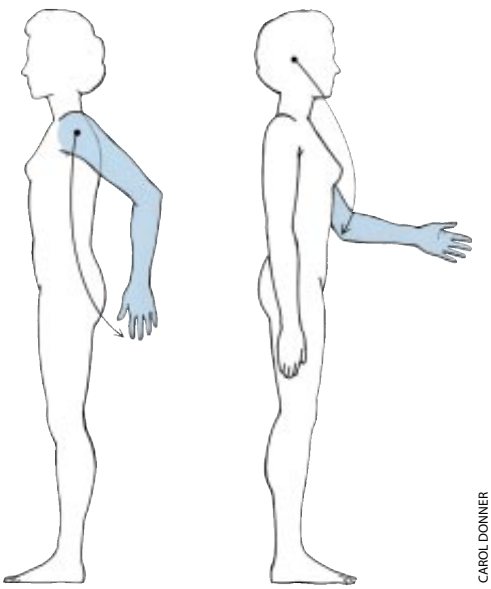
The specific neurosignature of an individual would be determined by the pattern of connectivity among neurons in the matrix—that is, by such factors as which neurons are connected to one another and by the number, types and strengths of the synapses. Readers familiar with neuroscience will note that my conception of the neuromatrix has similarities to the notion of the cell assembly proposed long ago by Donald O. Hebb of McGill University. Hebb argued that when sensory input activates two brain cells simultaneously, synapses between the cells form stronger connections. Eventually the process gives rise to whole assemblies of linked neurons, so that a signal going into one part of an assembly spreads through the rest, even if the assembly extends across broad areas of the brain.

I depart from Hebb, however, in that I visualize the neuromatrix as an assembly whose connections are primarily determined not by experience but by the genes. The matrix, though, could later be sculpted by experience, which would add or delete, strengthen or weaken, existing synapses. For instance, experience would enable the matrix to store the memory of a pain from a gangrenous ulcer and might thus account for the frequent reappearance of the same pain in phantom limbs.

I think the matrix is largely prewired, for the simple reason that my colleagues and I have encountered many people who were born without an arm or a leg and yet experience a vivid phantom. For example, an intelligent and serious eight-year-old boy, who was born with paralyzed legs and a right arm that ends at the elbow, tells us that when he fits his elbow into a small cup so as to manipulate a lever that allows him to move his wheelchair, phantom fingers, "like everyone else's fingers," emerge from his elbow and grasp the edges of the cup. Phantoms such as these may persist into adulthood: a 32-year-old engineer who was born without a leg below the knee reports that his phantom leg and foot remain vivid but vanish for several hours once or twice a week. He reports that he is always astonished and delighted when they return.

Parenthetically, I should note that the long-held belief that phantoms are experienced only when an amputation has occurred after the age of six or seven is not true. My postdoctoral student Renée Lacroix and I have confirmed earlier reports that children who lose a limb when they are as young as one or two years old can have phantom limbs. We have also encountered children who have painful phantoms of legs that were lost before age two.

Under normal circumstances, then, the myriad qualities of sensation people experience emerge from variations in sensory input. This input is both analyzed and shaped into complex experiences of sensation and self by the largely prewired neuromatrix. Yet even in the absence of external stimuli, much the same range of experiences can be generated by other signals passing through the neuromatrix—such as those produced by the spontaneous firing of neurons in the matrix itself or the spinal cord or produced by neuromas. Regardless of the source of the input to the matrix, the result would be the same: rapid spread of the signals throughout the matrix and perception of a limb that is located within a unitary



CAROL DONNER

REFERRED SENSATIONS in a painful phantom arm were reported by a woman receiving electrical stimuli at two points (*dots*). Stimulation at the stump gave the sensation of electric shocks that jumped from finger to finger. Stimulation on the right ear made the left phantom elbow feel warm and caused a pulsation that traveled down the phantom wrist and thumb. The observations were made by Joel Katz, now at the University of Toronto, and the author.

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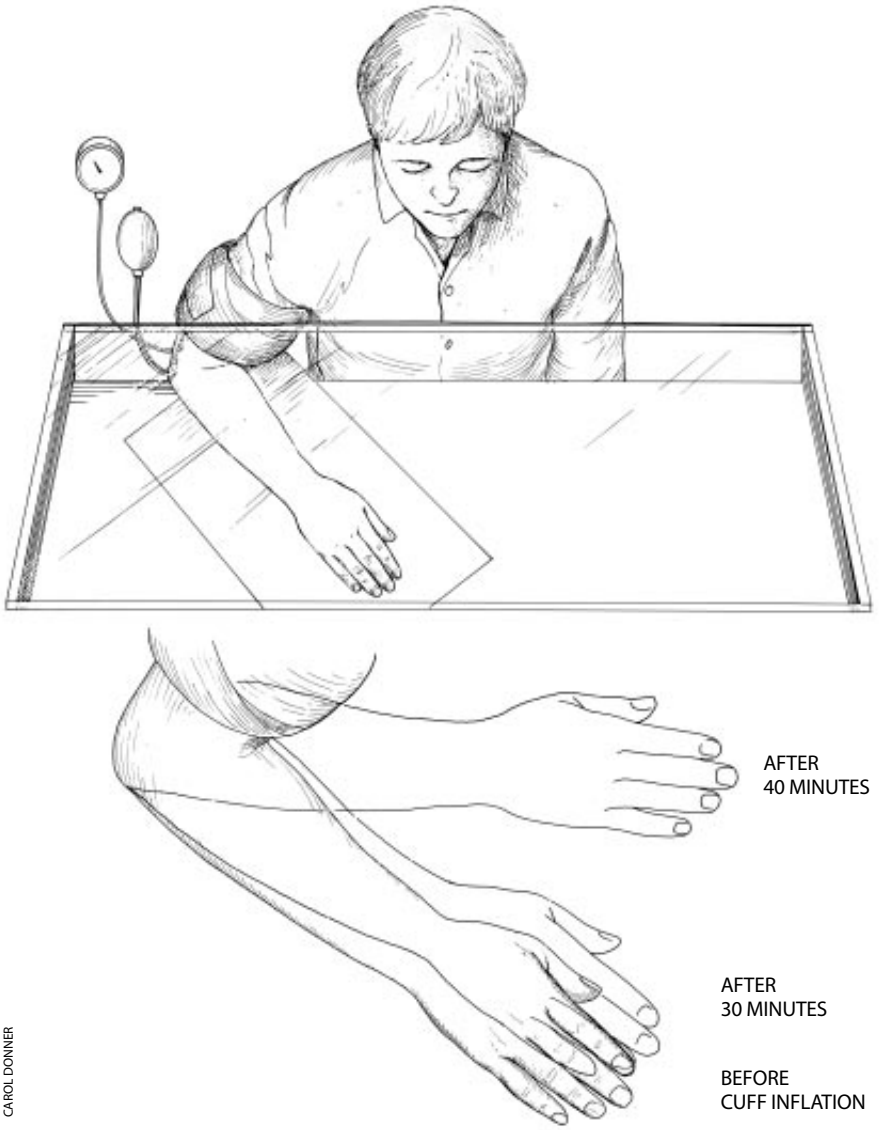

CAROL DONNER

REAL ARM made insensate by an inflated pressure cuff resembles a phantom arm. The subject could not see the arm, because the table was covered by a black cloth. The positions of the hand felt before the cuff was inflated and at intervals thereafter, as the hand seemed to be closer to the body, are shown. This study was carried out with Yigal Gross, now at Bar-Ilan University in Israel.

self, even when the actual limb is gone.

The fading of phantom limbs and their pain, which sometimes occurs over time, would be explained if cerebral neurons that once responded to lost or paralyzed limbs develop increasingly strong connections with still sensate parts of the body and then begin to serve those regions. In the process the neurosignature pattern would change, resulting in changes in the phantom and the pain. But phantoms do not usually disappear forever. In fact, they may return decades after they seem to have gone, which indicates that the neuromatrix, even when modified, retains many of its features permanently.

My students Anthony L. Vaccarino, John E. McKenna and Terence J. Coderre and I have already gathered some direct evidence supporting my suggestion that the brain—and by implication, the neuromatrix—can generate sensation on its own. Our studies relied on what is called the formalin pain test.

We injected a dilute solution of formalin (formaldehyde dissolved in water) under the skin of a rat's paw, which produces pain that rapidly rises and falls in intensity during the first five minutes after the injection. (The degree and duration of discomfort are assessed by such behaviors as licking the paw.) This "early" response is followed by "late" pain, which begins about 15 minutes after the injection and persists for about an hour.

By means of this test, we found that an anesthetic block of the paw completely obliterates the late pain, but only if the anesthetic is delivered in time to prevent the early response. Once the early pain occurs, the drug only partly reduces the later response. This observation of pain continuing even after the nerves carrying pain signals are blocked implies that long-lasting pain (such as that in phantoms) is determined not only by sensory stimulation during the discomfort but also by brain processes that persist without continual priming.

Phantom-Limb Pain

But what exactly causes the pain in phantom limbs? The most common complaint is a burning sensation. This feeling could stem from the loss of sensory signaling from the limb to the neuromatrix. Without its usual sensory stimulation, the neuromatrix would probably produce high levels of activity in a bursting pattern, such as Lenz observed in the thalamus. This kind of signal may very well be transformed into an awareness of burning.

Other pain may result from the effort of the neuromatrix to make the limbs move as they normally would. When the limbs do not respond in amputees and paraplegics, the neuromatrix (which would be prewired to "assume" the limbs can indeed move) may issue more frequent and stronger messages urging the muscles to move the limb. These outputs may be perceived as cramping. Similar output messages might also be felt as shooting pain.

Research to test some of these ideas and explore new ways of eliminating pain is still in its infancy, but some intriguing results are beginning to emerge. The need for such treatments is urgent, both because the suffering can be severe and persistent and because, sadly, few methods are permanently effective.

At the moment, a number of different therapies are used. Stimulation of the stump with electric currents, a vibrator or acupuncture helps some amputees. Relaxation and hypnosis aid others. Some individuals obtain considerable relief from drugs that are usually given to counteract epilepsy or depression, and other patients find their pain is eased by a combination of an antidepressant and a narcotic (such as methadone). But about half of those with persistent, long-term phantom pain fail to respond to any approach.

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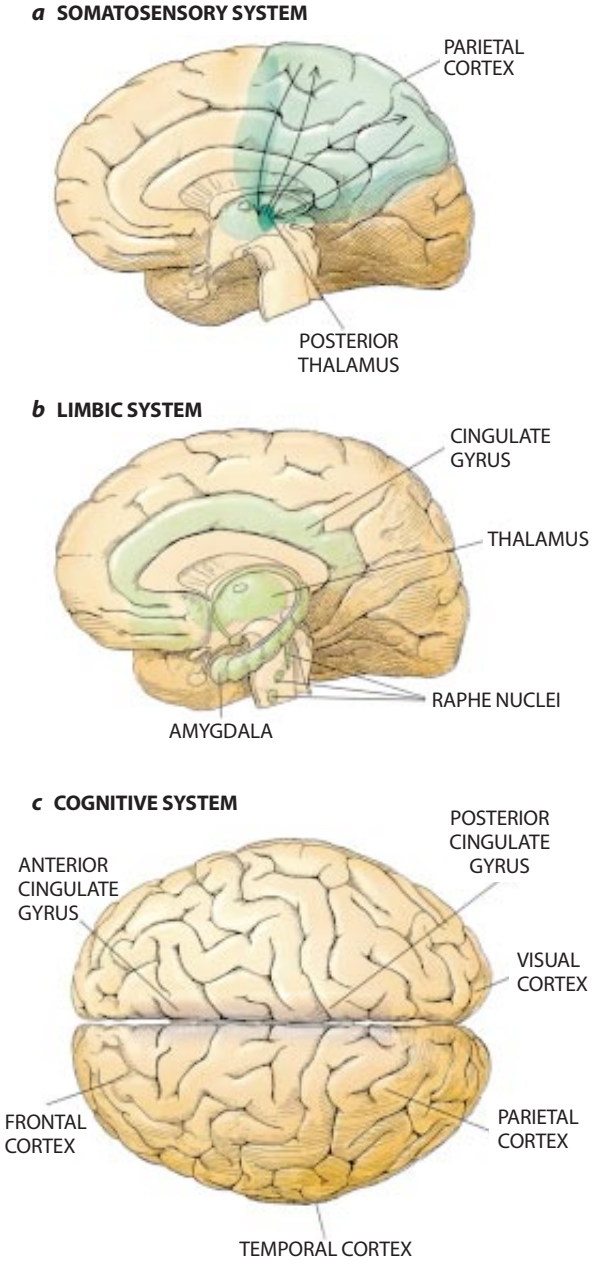

CAROL DONNER

SOURCE OF PHANTOM LIMBS is thought by the author to involve activity in three of the brain's neural circuits. One of them (*a*) is the somatosensory receiving areas and the adjacent parietal cortex, which process information related to the body. The second area (*b*) is the limbic system, which is concerned with emotion and motivation. The third (*c*) encompasses the widespread cortical networks involved in cognitive activities, among them the memory of past experience and the evaluation of sensory inputs in relation to the self.

On a more promising note, an experimental treatment called the DREZ (dorsal root entry zone) procedure selectively abolishes phantom-limb pain, but not the phantoms themselves, in about 60 percent of the patients treated. In this method, developed by Blaine S. Nashold of Duke University, neurosurgeons destroy the spinal cells that receive input directly from the sensory nerves of the stump, specifically eliminating the cells at the site where the sensory roots enter the spinal cord. (Past efforts at dampening the somatosensory projection system generally cut the sensory roots or the transmission pathways in the spinal cord.) The DREZ procedure is so new that no one yet knows how long the relief persists.

Because my model of brain functioning posits that the neuromatrix as a whole may contribute to pain, the model also suggests that altering the activity of pathways outside the somatosensory system might be important, either alone or in combination with other treatments. One place to begin work is the limbic system. Until now, limbic structures have been relegated to a secondary role in efforts to treat pain, because injurious stimuli do not activate them directly. Nevertheless, if the limbic system contributes to output by the neuromatrix, as I have proposed, it might well contribute to the pain felt in phantom limbs.

Vaccarino, McKenna, Coderre and I have begun to test the value of manipulating the limbic system as a way of easing pain. We have shown that localized injection of lidocaine (a relative of cocaine that prevents neurons from transmitting signals) into diverse areas of the limbic system produces striking decreases in several types of experimentally produced pain in rats, including a model of phantom-limb pain. A similar approach could be feasible for relieving phantom-limb pain in humans but needs more study.

The phenomenon of phantom limbs is more than a challenge to medical management. It raises doubts about some fundamental assumptions in psychology. One such assumption is that sensations are produced only by stimuli and that perceptions in the absence of stimuli are psychologically abnormal. Yet phantom limbs, as well as phantom seeing and hearing, indicate this notion is wrong. The brain does more than detect and analyze inputs; it generates perceptual experience even when no external inputs occur. We do not need a body to feel a body.

The Brain's Body Image

Another entrenched assumption is that perception of one's body results from sensory inputs that leave a memory in the brain; the total of these signals becomes the body image. But the existence of phantoms in people born without a limb or who have lost a limb at an early age suggests that the neural networks for perceiving the body and its parts are built into the brain. The absence of inputs does not stop the networks from generating messages about missing body parts; they continue to produce such messages throughout life.

In short, phantom limbs are a mystery only if we assume the body sends sensory messages to a passively receiving brain. Phantom limbs become comprehensible once we recognize that the brain generates the experience of the body. Sensory inputs merely modulate that experience; they do not directly cause it. SA

Further Reading

BODY IMAGE: DISSOCIATION OF REAL AND PERCEIVED LIMBS BY PRESSURE-CUFF ISCHEMIA. Y. Gross and R. Melzack in *Experimental Neurology,* Vol. 61, No. 3, pages 680–688; September 15, 1978.

PHANTOM LIMBS, THE SELF AND THE BRAIN: THE D. O. HEBB MEMORIAL LECTURE. R. Melzack in *Canadian Psychology,* Vol. 30, No. 1, pages 1–16; January 1989.

CENTRAL NERVOUS SYSTEM PLASTICITY IN THE TONIC PAIN RESPONSE TO SUBCUTANEOUS FORMALIN INJECTION. T. J. Coderre, A. L. Vaccarino and R. Melzack in *Brain Research,* Vol. 535, No. 1, pages 155–158; December 3, 1990.

PAIN "MEMORIES" IN PHANTOM LIMBS: REVIEW AND CLINICAL OBSERVATIONS. J. Katz and R. Melzack in *Pain,* Vol. 43, No. 3, pages 319–336; December 1990.

THE ROLE OF THE CINGULUM BUNDLE IN SELF-MUTILATION FOLLOWING PERIPHERAL NEURECTOMY IN THE RAT. A. L. Vaccarino and R. Melzack in *Experimental Neurology,* Vol. 111, No. 1, pages 131–134; January 1991.

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Autism

Autistic people suffer from a biological defect. Although they cannot be cured, much can be done to improve their lives

by Uta Frith

The Author

UTA FRITH is a senior scientist in the Cognitive Development Unit of the Medical Research Council in London. Born in Germany, she took a degree in psychology in 1964 at the University of the Saarland in Saarbrücken, where she also studied the history of art. Four years later she obtained her Ph.D. in psychology at the University of London. Besides autism, her interests include reading development and dyslexia. She has edited a book in the field of reading development, *Cognitive Processes in Spelling,* and is the author of *Autism: Explaining the Enigma.*

The "glass shell" metaphor for autism is misleading.

RODICA PRATO

The image often invoked to describe autism is that of a beautiful child imprisoned in a glass shell. For decades, many parents have clung to this view, hoping that one day a means might be found to break the invisible barrier. Cures have been proclaimed, but not one of them has been backed by evidence. The shell remains intact. Perhaps the time has come for the whole image to be shattered. Then at last we might be able to catch a glimpse of what the minds of autistic individuals are truly like.

Psychological and physiological research has shown that autistic people are not living in rich inner worlds but instead are victims of a biological defect that makes their minds very different from those of normal individuals. Happily, however, autistic people are not beyond the reach of emotional contact and attachment to others.

Thus, we can make the world more hospitable for autistic individuals just as we can, say, for the blind. To do so, we need to understand what autism is like—a most challenging task. We can imagine being blind, but autism seems unfathomable. For centuries, we have known that blindness is often a peripheral defect at the sensory-motor level of the nervous system, but only recently has autism been appreciated as a central defect at the highest level of cognitive processing. Autism, like blindness, persists throughout life, and it responds to special efforts in compensatory education. It can give rise to triumphant feats of coping but can also lead to disastrous secondary consequences—anxiety, panic and depression. Much can be done to prevent problems. Understanding the nature of the handicap must be the first step in any such effort.

Autism existed long before it was described and named by Leo Kanner of the Johns Hopkins Children's Psychiatric Clinic. Kanner published his landmark paper in 1943 after he had observed 11 children who seemed to him to form a recognizable group. All had in common four traits: a preference for aloneness, an insistence on sameness, a liking for elaborate routines and some abilities that seemed remarkable compared with the deficits.

Concurrently, though quite independently, Hans Asperger of the University Pediatric Clinic in Vienna prepared his doctoral thesis on the same type of child. He also used the term "autism" to refer to the core features of the disorder. Both men borrowed the label from adult psychiatry, where it had been used to refer to the progressive loss of contact with the outside world experienced by schizophrenics. Autistic children seemed to suffer such a lack of contact with the world around them from a very early age.

Kanner's first case, Donald, has long served as a prototype for diagnosis. It had been evident early in life that the boy was different from other children. At two years of age, he could hum and sing tunes accurately from memory. Soon he learned to count to 100 and to recite both the alphabet and the 25 questions and answers of the Presbyterian catechism. Yet he had a mania for making toys and other objects spin. Instead of playing like other toddlers, he arranged beads and other things in groups of different colors or threw them on the floor, delighting in the sounds they made. Words for him had a literal, inflexible meaning.

Donald was first seen by Kanner at age five. Kanner observed that the boy paid no attention to people around him. When someone interfered with his solitary activities, he was never angry with the interfering person but impatiently removed the hand that was in his way. His mother was the only person with whom he had any significant contact, and that seemed attributable mainly to the great effort she made to share activities with him. By the time Donald was about eight years old, his conversation consisted largely of repetitive questions. His relation to people remained limited to his immediate wants and needs, and his attempts at contact stopped as soon as he was told or given what he had asked for.

Some of the other children Kanner described were mute, and he found that even those who spoke did not really communicate but used language in a very odd way. For example, Paul, who was five, would parrot speech verbatim. He would say "You want

CHARACTERISTIC ALONENESS of autistic children is exhibited by a boy at the Association in Manhattan for Autistic Children, Inc. All the accompanying photographs were taken there.

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candy" when he meant "I want candy." He was in the habit of repeating, almost every day, "Don't throw the dog off the balcony," an utterance his mother traced to an earlier incident with a toy dog.

Twenty years after he had first seen them, Kanner reassessed the members of his original group of children. Some of them seemed to have adapted socially much better than others, although their failure to communicate and to form relationships remained, as did their pedantry and single-mindedness. Two prerequisites for better adjustment, though no guarantees of it, were the presence of speech before age five and relatively high intellectual ability. The brightest autistic individuals had, in their teens, become uneasily aware of their peculiarities and had made conscious efforts to conform. Nevertheless, even the best adapted were rarely able to be self-reliant or to form friendships. The one circumstance that seemed to be helpful in all the cases was an extremely structured environment.

As soon as the work of the pioneers became known, every major clinic began to identify autistic children. It was found that such children, in addition to their social impairments, have substantial intellectual handicaps. Although many of them perform relatively well on certain tests, such as copying mosaic patterns with blocks, even the most able tend to do badly on test questions that can be answered only by the application of common sense.

Autism is rare. According to the strict criteria applied by Kanner, it appears in four of every 10,000 births. With the somewhat wider criteria used in current diagnostic practice, the incidence is much higher: one or two in 1,000 births,

ABRAHAM MENASHE

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Autistic Behavior

The traits most characteristic of autistic people are aloneness, an insistence on sameness and a liking for elaborate routines. At the same time, some autistic individuals can perform complicated tasks, provided that the activity does not require them to judge what some other person might be thinking. These traits lead to characteristic forms of behavior, a number of which are portrayed here. —*U.F.*

Displays indifference

Indicates needs by using an adult's hand

Parrots words

Laughs and giggles inappropriately

Does not make eye contact

Does not pretend in playing

Joins in only if an adult insists and assists

Does not play with other children

Prefers sameness

Is one-sided in interactions

Talks incessantly about one topic

Behaves in bizarre ways

Handles or spins objects

Yet some do certain things well if the task does not involve social understanding.

RODICA PRATO

about the same as Down's syndrome. Two to four times as many boys as girls are affected.

For many years, autism was thought to be a purely psychological disorder without an organic basis. At first, no obvious neurological problems were found. The autistic children did not necessarily have low intellectual ability, and they often looked physically normal. For these reasons, psychogenic theories were proposed and taken seriously for many years. They focused on the idea that a child could become autistic because of some existentially threatening experience. A lack of maternal bonding or a disastrous experience of rejection, so the theory went, might drive an infant to withdraw into an inner world of fantasy that the outside world never penetrates.

These theories are unsupported by any empirical evidence. They are unlikely to be supported because there are many instances of extreme rejection and deprivation in childhood, none of which have resulted in autism. Unfortunately, therapies vaguely based on such notions are still putting pressure on parents to accept a burden of guilt for the supposedly avoidable and reversible breakdown of interpersonal interactions. In contrast, well-structured behavior modification programs have often helped fami-

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lies in the management of autistic children, especially children with severe behavior problems. Such programs do not claim to reinstate normal development in the children.

The insupportability of the psychogenic explanation of autism led a number of workers to search for a biological cause. Their efforts implicate a defective structure in the brain, but that structure has not yet been identified. The defect is believed to affect the thinking of autistic people, making them unable to evaluate their own thoughts or to perceive clearly what might be going on in someone else's mind.

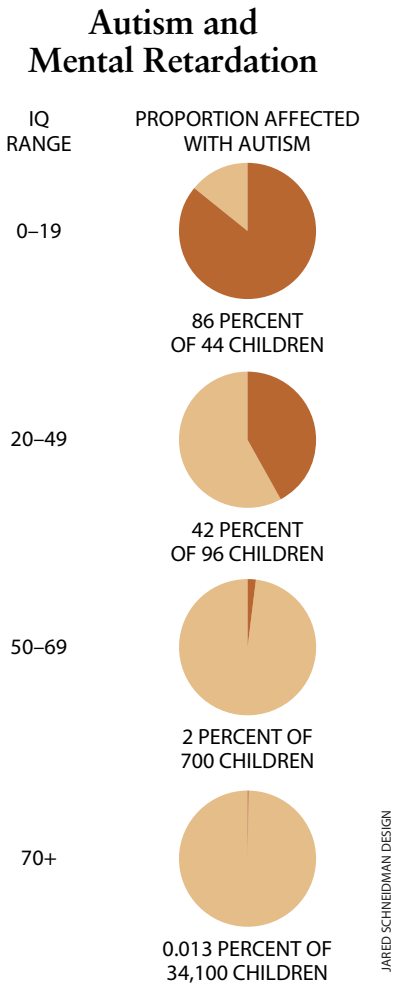
Autism appears to be closely associated with several other clinical and medical conditions. They include maternal rubella and chromosomal abnormality, as well as early injury to the brain and infantile seizures. Most impressive, perhaps, are studies showing that autism can have a genetic basis. Both identical twins are much more likely to be autistic than are both fraternal twins. Moreover, the likelihood that autism will occur twice in the same family is 50 to 100 times greater than would be expected by chance alone.

Defect in Frontal Lobes

Structural abnormalities in the brains of autistic individuals have turned up in anatomic studies and brain-imaging procedures. Both epidemiological and neuropsychological studies have demonstrated that autism is strongly correlated with mental retardation, which is itself clearly linked to physiological abnormality. This fact fits well with the idea that autism results from a distinct brain abnormality that is often part of more extensive damage. If the abnormality is pervasive, the mental retardation will be more severe, and the likelihood of damage to the critical brain system will increase. Conversely, it is possible for the critical system alone to be damaged. In such cases, autism is not accompanied by mental retardation.

Neuropsychological testing has also contributed evidence for the existence of a fairly circumscribed brain abnormality. Autistic individuals who are otherwise able show specific and extensive deficits on certain tests that involve planning, initiative and spontaneous generation of new ideas. The same deficits appear in patients who have frontal lobe lesions. Therefore, it seems plausible that whatever the defective brain structure or system is, the frontal lobes are implicated.

Population studies carried out by Lorna Wing and her colleagues at the Medical Research Council's Social Psychiatry Unit in London reveal that the different symptoms of autism do not occur together simply by coincidence. Three core features in particular—impairments in communication, imagination and socialization—form a distinct triad. The impairment in communication includes such diverse phenomena as muteness and delay in learning to talk, as well as problems in comprehending or using nonverbal body language. Other autistic individuals speak fluently but are overliteral in their understanding of language. The impairment in imagination appears in young autistic children as repetitive play with objects and in some autistic adults as an obsessive interest in facts. The impairment in socialization includes ineptness and inappropriate behavior in a wide range of reciprocal interactions, such as the ability to make and keep friends. Nevertheless, many autistic individuals prefer to have company and are eager to please.



SOURCE: Lorna Wing, Medical Research Council, London

CLOSE LINK between autism and mental retardation is reflected in this chart. The percentage of children showing the social impairments typical of autism is highest at low levels of intelligence as measured by tests in which an intelligence quotient (IQ) below 70 is subnormal. For example, 86 percent of 44 children in the lowest IQ range showed the social impairments of autism. The data are drawn from a population of about 35,000 children aged under 15 years.

The question is why these impairments, and only these, occur together. The challenge to psychological theorists was clear: to search for a single cognitive component that would explain the deficits yet still allow for the abilities that autistic people display in certain aspects of interpersonal interactions. My colleagues at the Medical Research Council's Cognitive Development Unit in London and I think we have identified just such a component. It is a cognitive mechanism of a highly complex and abstract nature that could be described in computational terms. As a shorthand, one can refer to this component by one of its main functions, namely, the ability to think about thoughts or to imagine another individual's state of mind. We propose that this component is damaged in autism. Furthermore, we suggest that this mental component is innate and has a unique brain substrate. If it were possible to pinpoint that substrate—whether it is in fact an anatomical structure, a physiological system or a chemical pathway—one might be able to identify the biological origin of autism.

The power of this component in normal development becomes obvious very early. From the end of the first year onward, infants begin to participate in what has been called shared attention. For example, a normal child will point to something for no reason other than to share his interest in it with someone else. Autistic children do not show shared attention. Indeed, the absence of this behavior may well be one of the earliest signs of autism. When an autistic child points at an object, it is only because he wants it.

In the second year of life, a particularly dramatic manifestation of the critical component can be seen in normal children: the emergence of pretense, or the ability to engage in fantasy and pretend play. Autistic children cannot un-

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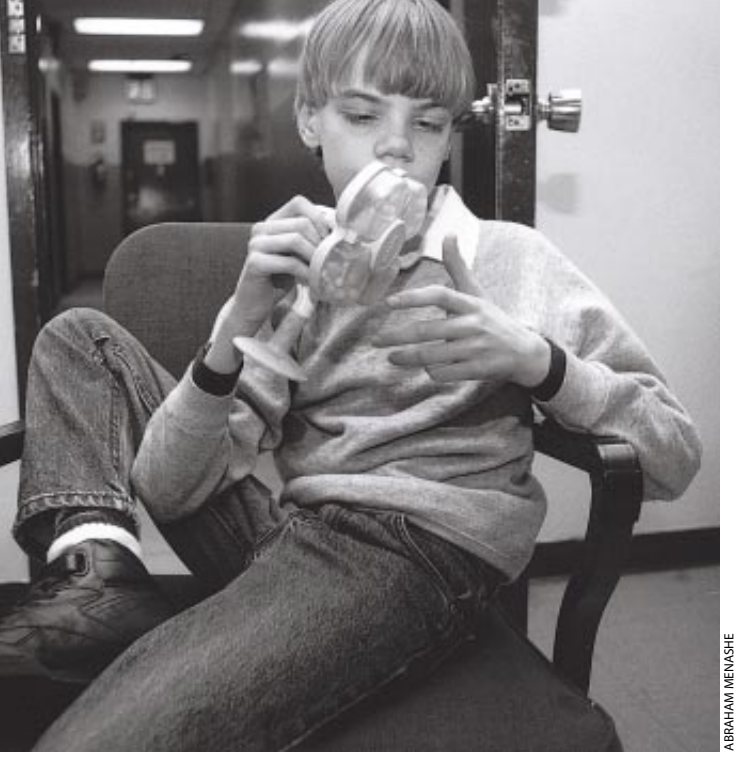

ABRAHAM MENASHE

UNUSUAL BEHAVIOR is often displayed by autistic individuals. Autistic children, for example, tend to fixate on making toys and other objects spin and to play repetitively.

derstand pretense and do not pretend when they are playing. The difference can be seen in such a typical nursery game as "feeding" a teddy bear or a doll with an empty spoon. The normal child goes through the appropriate motions of feeding and accompanies the action with appropriate slurping noises. The autistic child merely twiddles or flicks the spoon repetitively. It is precisely the absence of early and simple communicative behaviors, such as shared attention and make-believe play, that often creates the first nagging doubts in the minds of the parents about the development of their child. They rightly feel that they cannot engage the child in the emotional to-and-fro of ordinary life.

My colleague Alan M. Leslie devised a theoretical model of the cognitive mechanisms underlying the key abilities of shared attention and pretense. He postulates an innate mechanism whose function is to form and use what we might call second-order representations. The world around us consists not only of visible bodies and events, captured by first-order representations, but also of invisible minds and mental events, which require second-order representation. Both types of representation have to be kept in mind and kept separate from each other.

Second-order representations serve to make sense of otherwise contradictory or incongruous information. Suppose a normal child, Beth, sees her mother holding a banana in such a way as to be pretending that it is a telephone. Beth has in mind facts about bananas and facts about telephones—first-order representations. Nevertheless, Beth is not the least bit confused and will not start eating telephones or talking to bananas. Confusion is avoided because Beth computes from the concept of pretending (a second-order representation) that her mother is engaging simultaneously in an imaginary activity and a real one.

As Leslie describes the mental process, pretending should be understood as computing a three-term relation between an actual situation, an imaginary situation and an agent who does the pretending. The imaginary situation is then not treated as the real situation. Believing can be understood in the same way as pretending. This insight enabled us to predict that autistic children would not be able to understand that someone can have a mistaken belief about the world.

Together with our colleague Simon Baron-Cohen, we tested this prediction by adapting an experiment originally devised by two Austrian developmental psychologists, Heinz Wimmer and Josef Perner. The test has become known as the Sally-Anne task. Sally and Anne are playing together. Sally has a marble that she puts in a basket before leaving the room. While she is out, Anne moves the marble to a box. When Sally returns, wanting to retrieve the marble, she of course looks in the basket. If this scenario is presented as, say, a puppet show to normal children who are four years of age or more, they understand that Sally will look in the basket even though they know the marble is not there. In other words, they can represent Sally's erroneous belief as well as the true state of things. Yet in our test, 16 of 20 autistic children with a mean mental age of nine failed the task—answering that Sally would look in the box—in spite of being able to answer correctly a variety of other questions relating to the facts of the episode. They could not conceptualize the possibility that Sally believed something that was not true.

Many comparable experiments have been carried out in other laboratories, largely confirming our prediction: autistic children are specifically impaired in their understanding of mental states. They appear to lack the innate component underlying this ability. This component, when it works normally, has the most far-reaching consequences for higher-order conscious processes. It underpins the special feature of the human mind: the ability to reflect on itself. Thus, the triad of impairments in autism—in communication, imagination and socialization—is explained by the failure of a single cognitive mechanism. In everyday life, even very able autistic individuals find it hard to keep in mind simultaneously a reality and the fact that someone else may hold a misconception of that reality.

The automatic ability of normal people to judge mental states enables us to be, in a sense, mind readers. With sufficient experience we can form and use a theory of mind that allows us to speculate about psychological motives for our behavior and to manipulate other people's opinions, beliefs and attitudes. Autistic individuals lack the automatic ability to represent beliefs, and therefore they also lack a theory of mind. They cannot understand how behavior is caused by mental states or how beliefs and attitudes can be manipulated. Hence, they find it difficult to understand deception. The psychological undercurrents of real life as well as literature—in short, all that gives spice to social relations—for them remain a closed book. "People talk to each other with their eyes," said one observant autistic youth. "What is it that they are saying?"

Theory of Mind

Lacking a mechanism for a theory of mind, autistic children develop quite differently from normal ones. Most children acquire more and more sophisticated social and communicative skills as they develop other cognitive abilities. For example, children learn to be aware that there are faked and genuine expressions of feeling. Similarly, they become adept at that essential aspect of human communication—reading between the lines. They learn how to produce and

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understand humor and irony. In sum, our ability to engage in imaginative ideas, to interpret feelings and to understand intentions beyond the literal content of speech are all accomplishments that depend ultimately on an innate cognitive mechanism. Autistic children find it difficult or impossible to achieve any of these things. We believe this is because the mechanism is faulty.

This cognitive explanation for autism is specific. As a result, it enables us to distinguish the types of situations in which the autistic person will and will not have problems. It does not preclude

Explaining Autism's Variability

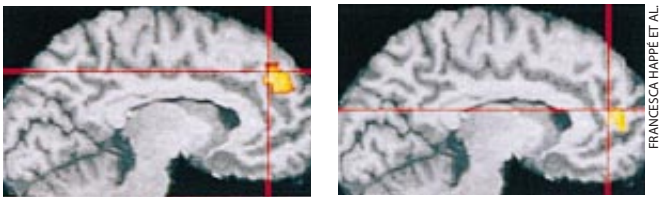
The astonishing variability in the signs and symptoms of autism is only beginning to be fully appreciated. Some autistic individuals never develop speech or nonverbal communication, whereas others become fluent and can pass for normal in social interactions. A screening test that identifies the lack of shared attention, pretend play and eye contact characteristic of autism—developed by Simon Baron-Cohen of the University of Cambridge and his colleagues at Guys Hospital in London—appears to be remarkably successful in predicting autism in children as young as 18 months.

The most severe cases of autism are associated with mental retardation, but IQ does not consistently correlate with abilities and special talents. Some studies report that up to 10 percent of the autistic population has a savant skill—exceptional ability in one area, such as playing the piano, drawing or mathematics. Significantly, almost all savants are diagnosed as autistic.

One of the most important advances in the field has been the growing recognition of a subgroup of autistic individuals who possess high verbal ability and develop a high degree of social awareness by utilizing an acquired, nonintuitive theory of mind. This variant of autism is called Asperger syndrome, and some individuals who exhibit it have successful academic careers in spite of their interpersonal communication problems, obsessive tendencies and restricted interests. Although autistic individuals with normal or higher IQs can show a high degree of social adaptation, even the most compensated have some difficulty in the give and take of everyday conversation and are unlikely to have intimate friends.

The theory of mind—that autistic individuals lack the ability to understand the role of mental states in others—proved to be a crucial step in explaining how the social and communication deficits of autism could coexist with good general abilities. This hypothesis also predicts that there is a specific substrate or pathway in the brain that gives us the ability to conceive of mental states, and recent brain imaging studies indicate that such an area may be located in the left medial prefrontal cortex. Yet the theory of mind is unable to account for all aspects of autism, such as stereotyped behavior and the desire for sameness or the exceptional talents present in a significant proportion of autistic individuals. Two additional hypotheses have been proposed.

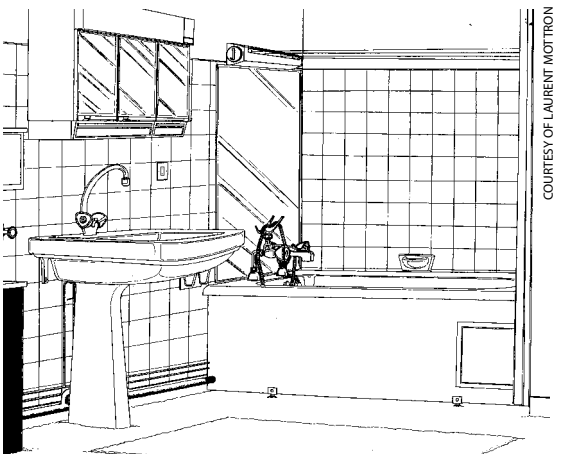
Bruce F. Pennington of the University of Denver and others in the U.S., as well as James Russell and his colleagues at the University of Cambridge in the U.K., have put forward the executive dysfunction hypothesis, which proposes that autistic individuals have a deficit in executive functions such as planning and working memory, impulse control, and initiation and monitoring of action. The processing of executive functions is thought to occur in the prefrontal cortex, and poor performance of these functions is directly related to repetitive thought and stereotyped, rigid behavior in autistic individuals.



FRANCESCA HAPPÉ ET AL.

BRAIN SCANS show differences in activity between normal and autistic people. In normal persons reading a story that requires inferring the mental state of others, the left medial prefrontal cortex of the brain was active (*left*). In persons with Asperger syndrome performing the same task, an adjacent lower area was active instead (*right*). The left medial prefrontal cortex may be a key component of the theory of mind capability.

Francesca Happé of London University and I have proposed the weak central coherence hypothesis as an explanation for the exceptional talents and restricted interests displayed by some autistic individuals. Weak central coherence refers to a preference by autistic individuals for segmental over holistic information processing. How the brain integrates information is obscure, but long-range connections between the hemispheres may well be involved. There is some evidence that people with autism process information in piecemeal fashion—the total attention of the autistic individual often is captured by fragments or selective features usually of little interest to normal persons. Surprisingly, autistic persons tend to be less susceptible to visual illusions, perhaps because they are less affected by the context in which the figure is embedded.



COURTESY OF LAURENT MOTTRON

FREEHAND DRAWING by E.C., a male autistic savant, was made spontaneously and without any corrections. Although the perspective appears realistic, it is achieved without the "vanishing points" most artists would need. Studies by Laurent Mottron and Sylvie Belleville of the University of Montreal show that E.C.'s ability to integrate parts of visual patterns is impaired; he is unable to reproduce anything resembling a human face but has exceptional ability to remember and draw individual objects and geometric shapes.

Because it provides a model for the ability to conceive of mental states, research into autism is stimulating philosophical debate on self-consciousness. Future studies may lead to the identification of subcomponents or precursors of consciousness in other species, which in turn might lead to a better understanding of the development of conscious experience in humans. *—U.F.*

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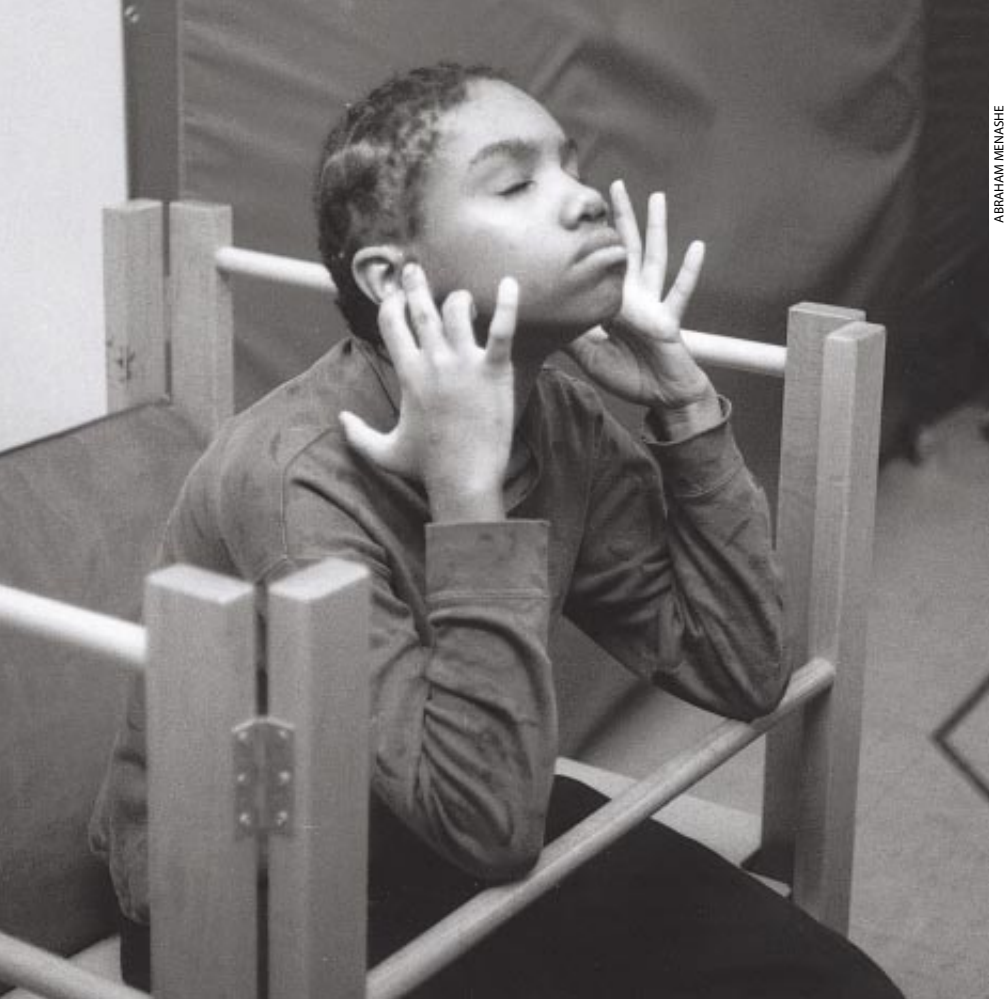

ABRAHAM MENASHE

SELF-ABSORPTION displayed by this autistic girl is a common feature of the disorder. In the motion picture *Rain Man,* self-absorption was the key trait of the central character, an autistic adult portrayed by actor Dustin Hoffman.

the existence of special assets and abilities that are independent of the innate mechanism my colleagues and I see as defective. Thus it is that autistic individuals can achieve social skills that do not involve an exchange between two minds. They can learn many useful social routines, even to the extent of sometimes camouflaging their problems. The cognitive deficit we hypothesize is also specific enough not to preclude high achievement by autistic people in such diverse activities as musical performance, artistic drawing, mathematics and memorization of facts.

It remains to be seen how best to explain the coexistence of excellent and abysmal performance by autistic people in abilities that are normally expected to go together. It is still uncertain whether there may be additional damage to emotions that prevents some autistic children from being interested in social stimuli. We have as yet little idea what to make of the single-minded, often obsessive, pursuit of certain activities. With the autistic person, it is as if a powerful integrating force—the effort to seek meaning—were missing.

Helping the Handicapped

The old image of the child in the glass shell is misleading in more ways than one. It is incorrect to think that inside the glass shell is a normal individual waiting to emerge, nor is it true that autism is a disorder of childhood only. The motion picture *Rain Man* came at the right time to suggest a new image to a receptive public. Here we see Raymond, a middle-aged man who is unworldly, egocentric in the extreme and all too amenable to manipulation by others. He is incapable of understanding his brother's double-dealing pursuits, transparently obvious though they are to the cinema audience. Through various experiences it becomes possible for the brother to learn from Raymond and to forge an emotional bond with him. This is not a farfetched story. We can learn a great deal about ourselves through the phenomenon of autism.

Yet the illness should not be romanticized. We must see autism as a devastating handicap without a cure. The autistic child has a mind that is unlikely to develop self-consciousness. But we can now begin to identify the particular types of social behavior and emotional responsiveness of which autistic individuals are capable. Autistic people can learn to express their needs and to anticipate the behavior of others when it is regulated by external, observable factors rather than by mental states. They can form emotional attachments to others. They often strive to please and earnestly wish to be instructed in the rules of person-to-person contact. There is no doubt that within the stark limitations a degree of satisfying sociability can be achieved.

Autistic aloneness does not have to mean loneliness. The chilling aloofness experienced by many parents is not a permanent feature of their growing autistic child. In fact, it often gives way to a preference for company. Just as it is possible to engineer the environment toward a blind person's needs or toward people with other special needs, so the environment can be adapted to an autistic person's needs.

On the other hand, one must be realistic about the degree of adaptation that can be made by the limited person. We can hope for some measure of compensation and a modest ability to cope with adversity. We cannot expect autistic individuals to grow out of the unreflecting mind they did not choose to be born with. Autistic people in turn can look for us to be more sympathetic to their plight as we better understand how their minds are different from ours. SA

Further Reading

AUTISM: EXPLAINING THE ENIGMA. Uta Frith. Blackwell Publishers, 1989.

THE COGNITIVE BASIS OF A BIOLOGICAL DISORDER: AUTISM. Uta Frith, John Morton and Alan M. Leslie in *Trends in Neurosciences*, Vol. 14, No. 10, pages 433-438; October 1991.

AUTISM AND ASPERGER SYNDROME. Edited by Uta Frith. Cambridge University Press, 1992.

UNDERSTANDING OTHER MINDS: PERSPECTIVES FROM AUTISM. Edited by Simon Baron-Cohen, Helen Tager-Flusberg and Donald J. Cohen. Oxford University Press, 1993.

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Seeking the Criminal Element

by W. Wayt Gibbs, *staff writer*

Scientists are homing in on social and biological risk factors that they believe predispose individuals to criminal behavior. The knowledge could be ripe with promise—or rife with danger

Imagine you are the father of an eight-year-old boy," says psychologist Adrian Raine, explaining where he believes his 17 years of research on the biological basis of crime is leading. "The ethical dilemma is this: I could say to you, 'Well, we have taken a wide variety of measurements, and we can predict with 80 percent accuracy that your son is going to become seriously violent within 20 years. We can offer you a series of biological, social and cognitive intervention programs that will greatly reduce the chance of his becoming a violent offender.' What do you do? Do you place your boy in those programs and risk stigmatizing him as a violent criminal even though there is a real possibility that he is innocent? Or do you say no to the treatment and run an 80 percent chance that your child will grow up to (a) destroy his life, (b) destroy your life, (c) destroy the lives of his brothers and sisters and, most important, (d) destroy the lives of the innocent victims who suffer at his hands?"

For now, such a choice is purely hypothetical. Scientists cannot yet predict which children will become dangerously aggressive with anything like 80 percent accuracy. But increasingly, those who study the causes of criminal and violent behavior are looking beyond broad demographic characteristics such as age, race and income level to factors in individuals' personality, history, environment and physiology that seem to put them—and society—at risk. As sociologists reap the benefits of rigorous long-term studies and neuroscientists tug at the tangled web of relations between behavior and brain chemistry, many are optimistic that science will identify markers of maleficence. "This research might not pay off for 10 years, but in 10 years it might revolutionize our criminal justice system," asserts Roger D. Masters, a political scientist at Dartmouth College.

Preventive Intervention

With the expected advances, we're going to be able to diagnose many people who are biologically brain-prone to violence," claims Stuart C. Yudofsky, chair of the psychiatry department at Baylor College of Medicine and editor of the *Journal of Neuropsychiatry and Clinical Neurosciences*. "I'm not worried about the downside as much as I am encouraged by the opportunity to prevent tragedies—to screen people who might have high risk and to prevent them from harming someone else." Raine, Yudofsky and others argue that in order to control violence, Americans should trade their traditional concept of justice based on guilt and punishment for a "medical model" based on prevention, diagnosis and treatment.

But many scientists and observers do worry about a downside. They are concerned that some researchers underplay the enormous complexity of individual behavior and overstate sci-

BRUCE DAVIDSON *Magnum*

TEXAN TEENS playing with gang signs and loaded guns are acting their age—most adolescents dabble in delinquency for several years. But a small fraction grow into the chronic felons that commit the majority of violent crimes. Can scientists identify the dangerous few before they attack—and if so, what then?

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entists' ability to understand and predict it. They also fear that a society desperate to reduce crime might find the temptation to make premature use of such knowledge irresistible.

Indeed, the history of science's assault on crime is blemished by instances in which incorrect conclusions were used to justify cruel and unusual punishments. In the early 1930s, when the homicide rate was even higher than it is today, eugenics was in fashion. "The eugenics movement was based on the idea that certain mental illness and criminal traits were all inherited," says Ronald L. Akers, director of the Center for Studies in Criminology and Law at the University of Florida. "It was based on bad science, but they thought it was good science at the time." By 1931, 27 states had passed laws allowing compulsory sterilization of "the feeble-minded," the insane and the habitually criminal.

Studies in the late 1960s—when crime was again high and rising—revealed that many violent criminals had an extra Y chromosome and thus an extra set of "male" genes. "It was a dark day for science in Boston when they started screening babies for it," recalls Xandra O. Breakefield, a geneticist at Massachusetts General Hospital. Subsequent studies revealed that although XYY men tend to score lower on IQ tests, they are not unusually aggressive.

Social science studies on the causes of crime have been less controversial, in part because they have focused more on populations than on individuals. But as consensus builds among criminologists on a few key facts, researchers are assembling these into prediction models that try to identify the juveniles most likely to lapse into delinquency and then into violent crime.

Perhaps their most consistent finding is that a very small number of criminals are responsible for most of the violence.

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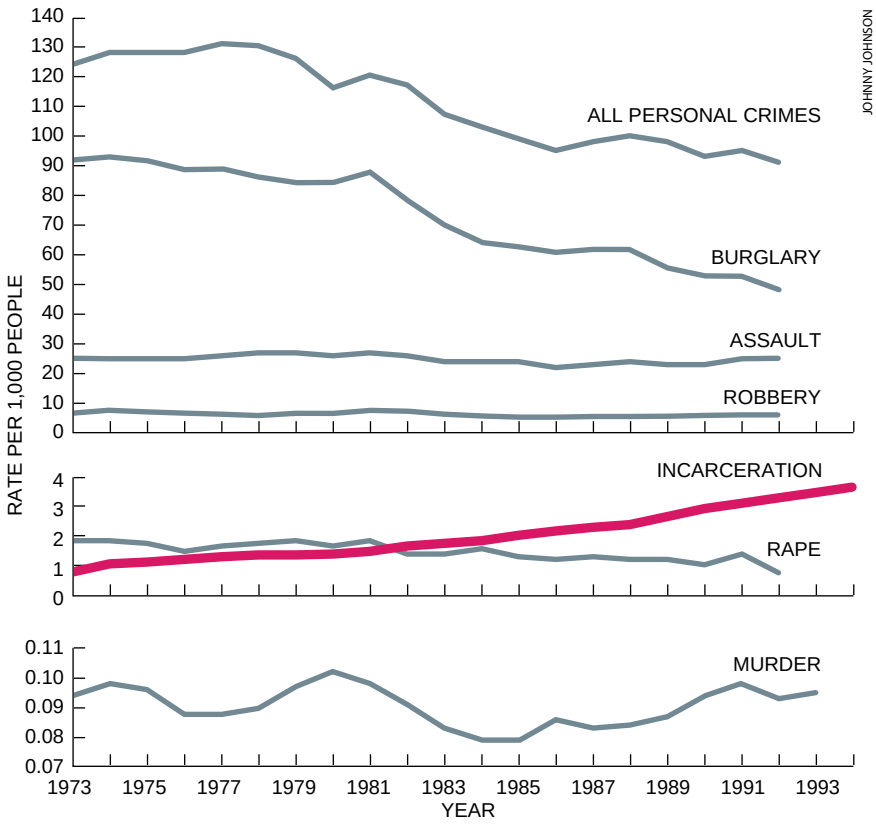

SOURCE: Bureau of Justice Statistics, U.S. Department of Justice

CRIME RATES have not responded consistently to "get tough" approaches to incarceration. Since the early 1970s the proportion of Americans behind bars has more than tripled. Property crime (including burglary, robbery and personal larceny) has dropped about 30 percent, but violent crime remains high.

One study, for example, tracked for 27 years 10,000 males born in Philadelphia in 1945; it found that just 6 percent of them committed 71 percent of the homicides, 73 percent of the rapes and 69 percent of the aggravated assaults attributed to the group.

Preventing just a small fraction of adolescent males from degenerating into chronic violent criminals could thus make a sizable impact on the violent crime rate, which has remained persistently high since 1973 despite a substantial decline in property crime. (Females accounted for only 12.5 percent of violent crime in 1992.) "For every 1 percent that we reduce violence, we save the country $1.2 billion," Raine asserts.

The problem, says Terrie E. Moffitt, a psychologist at the University of Wisconsin who is conducting long-term delinquency prediction studies, is that "a lot of adolescents participate in antisocial behavior"—87 percent, according to a survey of U.S. teens. "The vast majority desist by age 21," she says. The dangerous few "are buried within that population of males trying out delinquency. How do you pick them out? Our hypothesis is that those who start earliest are at highest risk."

Marion S. Forgatch of the Oregon Social Learning Center tested that hypothesis on 319 boys from high-crime neighborhoods in Eugene. At the November 1994 American Society of Criminology meeting, she reported her findings: boys who had been arrested by age 14 were 17.9 times more likely to become chronic offenders than those who had not, and chronic offenders were 14.3 times more likely to commit violent offenses. "This is a good way of predicting," she says.

False Positive ID

Good is a relative term. For if one were to predict that every boy in her study who was arrested early would go on to commit violent crimes, one would be wrong more than 65 percent of the time. To statisticians, those so misidentified are known as false positives. "All of these predictors have a lot of false positives—about 50 percent on average," says Akers, who recently completed a survey of delinquency prediction models. Their total accuracy is even lower, because the models also fail to identify some future criminals.

The risk factors that Akers says researchers have found to be most closely associated with delinquency are hardly surprising. Drug use tops the list, followed by family dysfunction, childhood behavior problems, deviant peers, poor school performance, inconsistent parental supervision and discipline, separation from parents, and poverty. Numerous other controlled studies have found that alcoholism, childhood abuse, low verbal IQ and witnessing violent acts are also significant risk factors. Compared with violent behavior, however, all these experiences are exceedingly common. The disparity makes it very difficult to determine which factors are causes and which merely correlates.

The difference is important, notes Mark W. Lipsey of Vanderbilt University, because "changing a risk factor if it is not causal may have no impact," and the ultimate goal of prediction is to stop violence by intervening before it begins. Unfortunately, improvements in predictive models do not necessarily translate into effective intervention strategies. Lipsey recently analyzed how well some 500 delinquency treatment programs reduced recidivism. "The conventional wisdom that nothing works is just wrong," he concludes. But he concedes that "the net effect is modest"—on average, 45 percent of program participants were rearrested, versus 50 percent of those left to their own devices. Half of that small apparent improvement, he adds, may be the result of inconsistency in the methods used to evaluate the programs.

Some strategies do work better than others, Lipsey discovered. Behavioral programs that concentrated on teaching job skills and rewarding prosocial attitudes cut rearrest rates to about 35 percent. "Scared straight" and boot camp programs, on the other hand, tended to increase recidivism slightly.

Patrick H. Tolan of the University of Illinois at Chicago has also recently published an empirical review of delinquency programs. To Lipsey's findings he adds that "family interventions have repeatedly shown efficacy for reducing antisocial behavior and appear to be among the most promising interven-

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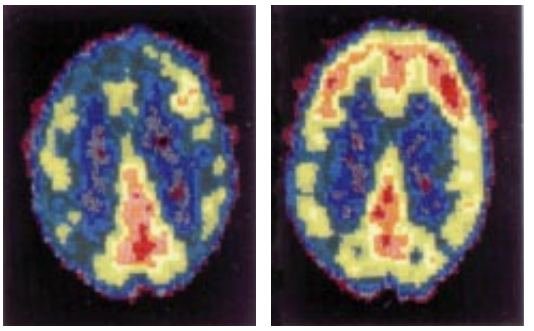
tions to date." According to Forgatch, two experiments in Eugene, Ore., showed that teaching parents better monitoring and more consistent, less coercive discipline techniques reduces their kids' misbehavior. "We should make parenting skills classes compulsory for high school students," argues Raine of the University of Southern California.

Unfortunately, Tolan observes, family intervention is difficult and rarely attempted. The most common kinds of programs—counseling by social workers, peer mediation and neighborhood antiviolence initiatives—are hardly ever examined to see whether they produce lasting benefits. "It usually is hard to imagine that a good idea put into action by well-meaning and enlightened people cannot help," he noted in the paper. "It may seem that any effort is better than nothing. Yet our review and several of the more long-term and sophisticated analyses suggest that both of these assumptions can be dangerously wrong. Not only have programs that have been earnestly launched been ineffective, but some of our seemingly best ideas have led to worsening of the behavior of those subjected to the intervention."

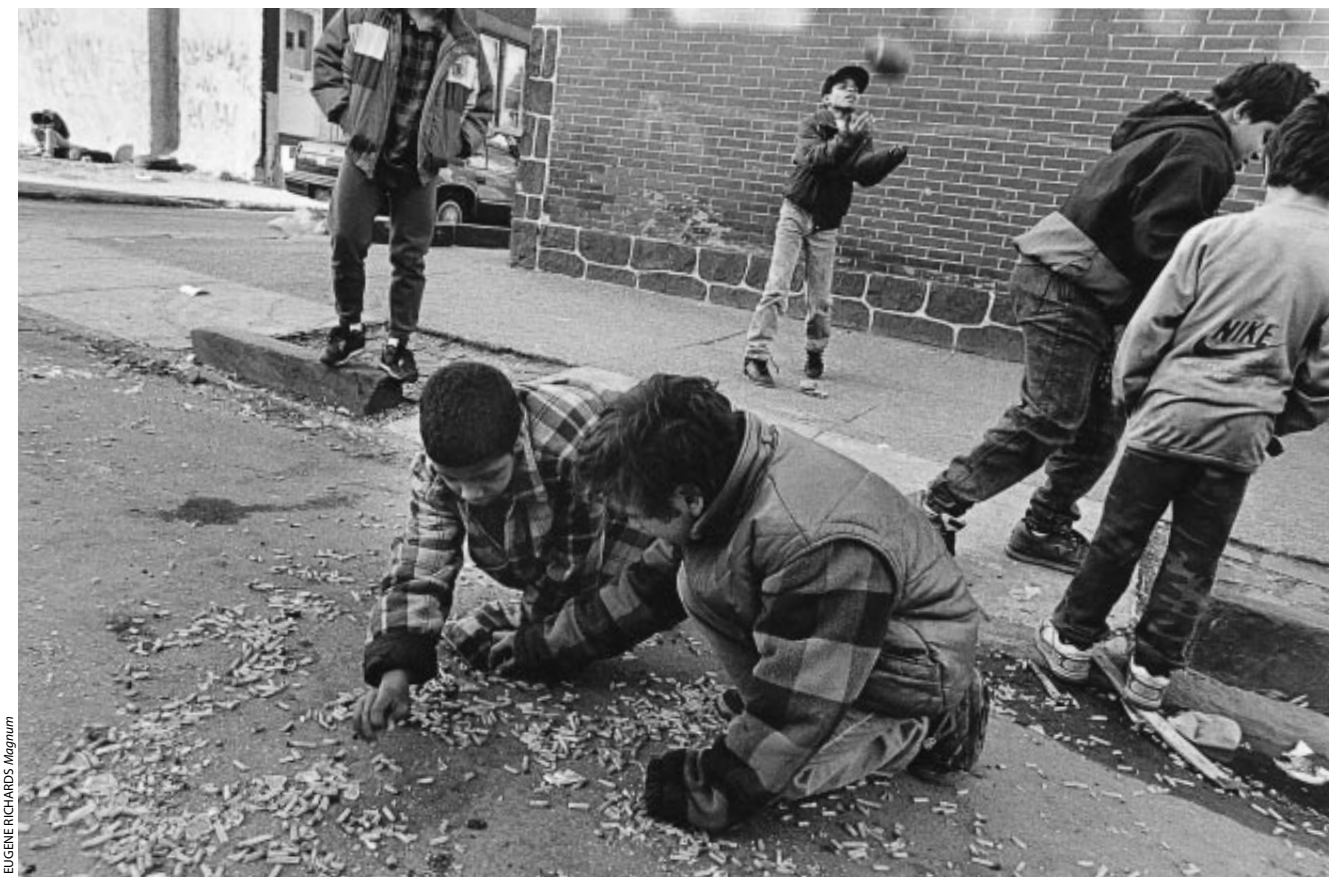
Many researchers are thus frustrated that the Violent Crime Control and Law Enforcement Act of 1994 puts most of its $6.1 billion for crime prevention in untested and controversial programs, such as "midnight basketball" and other after-school activities. "Maybe these programs will help; maybe they won't," Tolan says. "No one has done a careful evaluation." The Crime Act does not insist that grant applicants demonstrate or even measure the effectiveness of their approach. For these and other reasons, Republicans vowed in their 1994 "Contract with America" to repeal all prevention programs in the Crime Act and to increase funding for prison construction. But that strategy ignored research. "We do know," Tolan asserts, "that locking kids up will not reduce crime and may eventually make the problem worse."



ADRIAN RAINE AND MONTE S. BUCHSBAUM

BRAIN OF MURDERER (*left*) **shows less activity in the frontal cortex** (*top third of image*) **than the brain of a nonviolent subject of the same age and sex. In one study of 22 murderers, about 75 percent had low frontal activity, which is believed to indirectly regulate aggressive impulses.**

The failure of sociology to demonstrate conclusively effective means of controlling violent crime has made some impatient. "There is a growing recognition that we're not going to solve any problem in society using just one discipline," says Diana Fishbein, a professor of criminology at the University of Baltimore. "Sociological factors play a role. But they have not been able to explain



EUGENE RICHARDS *Magnum*

POOR PARENTAL SUPERVISION is a major risk factor for later delinquency. These children in Philadelphia play with empty crack cocaine vials. Parent training programs have been among the most successful in reducing kids' antisocial behavior.

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The Tangled Roots of Violence

The failure of expensive prison booms and welfare programs to beat back the historically high violent crime rates of the past 20 years has prepared fertile ground for new approaches to crime control. Encouraged by research that tentatively links a few instances of antisocial aggression with biological abnormalities, some politicians and activists are turning to science, perhaps too hastily, to identify and treat those who are likely to become dangerous.

Take the case of Everett L. "Red" Hodges, a California oilman who has spent more than $1 million to support research that implicates the trace metal manganese as a marker for violent criminal behavior. Hodges was struggling to tame a delinquent son in 1984 when he came across a *Science News* story on a study that had found high levels of lead, cadmium and copper in the head hair of violent felons.

Intrigued, Hodges offered funding to Louis A. Gottschalk, a psychiatrist at the University of California at Irvine, to conduct a controlled study to replicate the results. Analysis of hair clipped from convicted and accused felons at a prison and two county jails in southern California revealed no unusual levels of lead, cadmium or copper. But Gottschalk did find that average levels of manganese were about 3.6 times higher in the alleged felons than in men of similar age and race at local barbershops. "A new paradigm is opening in criminal justice," Hodges says, beaming. "It's a marker."

KELLY NEWS AND ENTERTAINMENT *KCRA, Sacramento*

EVERETT L. "RED" HODGES discusses on television the results of a nutritional study on inmate behavior.

That judgment may be premature. Critics of Gottschalk's research, published in 1991 in a psychiatric (rather than a nutrition) journal, point out that average manganese levels varied from 2.2 parts per million in the prisoners to just 0.71 in one of the groups of jail inmates. Previous studies had found *lower* manganese levels in inmates than in control subjects. Skeptics also note that Gottschalk threw a wide net, measuring levels of 23 trace metals. "If you look at enough variables, you're bound to find a statistically significant association," comments Curtiss D. Hunt of

why one person becomes violent and another doesn't."

Some social scientists are looking to psychiatrists, neurologists and geneticists to provide answers to that question, ready or not. "Science must tell us what individuals will or will not become criminals, what individuals will or will not become victims, and what law enforcement strategies will or will not work," wrote C. Ray Jeffery, a criminologist at Florida State University, in 1994 in the *Journal of Research in Crime and Delinquency.*

Biological Factors

As medical researchers have teased out a few tantalizing links between brain chemistry, heredity, hormones, physiology and assaultive behavior, some have become emboldened. "Research in the past 10 years conclusively demonstrates that biological factors play some role in the etiology of violence. That is scientifically beyond doubt," Raine holds forth. The importance of that role is still very much in doubt, however.

As with social risk factors, no biological abnormality has been shown to *cause* violent aggression—nor is that likely except in cases of extreme psychiatric disorder. But researchers have spotted several unusual features, too subtle even to be considered medical problems, that tend to appear in the bodies and brains of physically aggressive men. On average, for example, they have higher levels of testosterone, a sex hormone important for building muscle mass and strength, among other functions. James M. Dabbs, Jr., of Georgia State University has found in his experiments with prison inmates that men with the highest testosterone concentrations are more likely to have committed violent crimes. But Dabbs emphasizes that the link is indirect and "mediated by many social factors," such as higher rates of divorce and substance abuse.

"Low resting heart rate probably represents the best replicated biological correlate of antisocial behavior," Raine observes, pointing to 14 studies that have found that problem children and petty criminals tend to have significantly lower pulses than do well-behaved counterparts. A slower heartbeat "probably reflects fearlessness and underarousal," Raine theorizes. "If we lack

EUGENE RICHARDS *Magnum*

SINS OF THE PARENT are often visited on the child. Delinquents are more likely to have parents who abuse drugs or alcohol, commit crimes or beat them. But risk factors are generally poor predictors: most children of such parents do not become chronic criminals.

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the Grand Forks Human Nutrition Research Center in North Dakota. "But it may be meaningless." Hunt adds that the concentration of a metal in the hair does not tell one how much is in the blood or the brain. "We know so little about manganese's role in the body that we haven't even set an RDA [recommended daily allowance] for it."

Hodges remains convinced he is on the right track. "Violence can be detected and treated," he argues. In 1987 a mugger fractured the skull of another of Hodges's sons. That year Hodges founded the Violence Research Foundation (VRF) to lobby public officials to experiment with treatment programs that use what he calls "the power of nutrition" to pacify violent criminals.

The VRF found an ally in Senator Robert Presley of California, who pushed through a bill in 1989 authorizing a study of male prisoners by Stephen Schoenthaler of California State University at Stanislaus. In the first part of the study, 402 offenders were divided randomly into three groups and given vitamin-mineral supplements equivalent to the RDA, three times the RDA or a placebo. Preliminary results showed that rule violations among the first group dropped 38 percent during the study. Strangely, the behavior of inmates getting the higher dose did not improve significantly, whereas violations rose 20 percent among the placebo group.

Trace element deficiencies are just one of many frequently cited but poorly demonstrated claims that nutritional problems can cause criminal and violent behavior.

Although encouraging, the equivocal results were so inconclusive that Schoenthaler decided not to publish them until he completed further studies with more controls. Hodges, however, publicized the results widely at conferences and on television talk shows, much to the scientist's annoyance.

Trace element deficiencies are just one of many frequently cited but poorly demonstrated claims that nutritional problems can cause criminal and violent behavior. A 1992 report by the Federal Bureau of Prisons stated that correctional facilities in 46 states have incorporated a wide array of dietary intervention and testing programs, even though "such programs are perceived by many physicians, scientific researchers, registered dietitians, and other health care professionals as an incorporation of food faddism into public policy." *—Steven Vames and W. Wayt Gibbs*

the fear of getting hurt, it may lead to a predisposition to engage in violence." But that hypothesis fails to explain why at least 15 studies have failed to find abnormal heart rates in psychopaths.

Jerome Kagan, a Harvard University psychologist, has suggested that an inhibited "temperament" may explain why the great majority of children from high-risk homes grow up to become law-abiding citizens. One study tested pulse, pupil dilation, vocal tension and blood levels of the neurotransmitter norepinephrine and the stress-regulating hormone cortisol to distinguish inhibited from uninhibited, underaroused two-year-olds. An expert panel on "Understanding and Preventing Violence" convened by the National Research Council suggested in its 1993 report that inhibited children may be protected by their fearfulness from becoming aggressive, whereas uninhibited children may be prone to later violence. The panel concluded that "although such factors in isolation may not be expected to be strong predictors of violence, in conjunction with other early family and cognitive measures, the degree of prediction may be considerable."

Perhaps the most frequently cited biological correlate of violent behavior is a low level of serotonin, a chemical that in the body inhibits the secretion of stomach acid and stimulates smooth muscle and in the brain functions as a neurotransmitter. A large body of animal evidence links low levels of serotonin to impulsive aggression. Its role in humans is often oversimplified, however. "Serotonin has a calming effect on behavior by reducing the level of violence," Jeffery wrote in 1993 in the *Journal of Criminal Justice Education*. "Thus, by increasing the level of serotonin in the brain, we can reduce the level of violence." A front-page article in December 1993 in the *Chicago Tribune* explained that "when serotonin declines… impulsive aggression is unleashed."

Such explanations do violence to the science. In human experiments, researchers do not generally have access to the serotonin inside their subject's braincase. Instead they tap cerebrospinal fluid from the spinal column and measure the concentration of 5-hydroxyindoleacetic acid (5-HIAA), which is produced when serotonin is used up and broken down by the enzyme monoamine oxidase (MAO). Serotonin does its job by

STEPHEN SHAMES *Matrix*

CHILDHOOD AGGRESSIVENESS, seen in this boy threatening his brother with a broom, is one of the strongest known predictors of later violence. Yet in 1990 a 17-year study found that of 209 hyperaggressive preschoolers predicted to develop antisocial behavior, 177 did not.

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ANDREW LICHTENSTEIN *Impact Visuals*

KENNETH JARECKE *Contact Press Images*

STEPHEN SHAMES *Matrix*

SOCIAL RISK FACTORS that seemingly push youths toward violent behavior include repeatedly witnessing assaults, heavy drinking or drug use (implicated in about 60 percent of all offenses), association with deviant peers and gun possession. Shown here are underage drinking in New York City (*above, left*), boys in Omaha detained after a drive-by shootout (*above, right*) and the aftermath of a shooting in Houston (*left*).

binding to any of more than a dozen different neural receptors, each of which seems to perform a distinct function. The low levels of 5-HIAA seen in violent offenders may indicate a shortage of serotonin in the brain or simply a dearth of MAO—in which case their serotonin levels may actually be high. Moreover, serotonin can rise or drop in different regions of the brain at different times, with markedly different effects.

Environment, too, plays a role: nonhuman primate studies show that serotonin often fluctuates with pecking order, dropping in animals when they are threatened and rising when they assume a dominant status. The numerous pathways through which serotonin can influence mood and behavior confound attempts to simply "reduce the level of violence" by administering serotonin boosters such as Prozac, a widely prescribed antidepressant. Nevertheless, the link between 5-HIAA and impulsive aggression has led to a concerted hunt for the genes that control the production and activity of serotonin and several other neurotransmitters. "Right now we have in our hand many of the genes that affect brain function," says David Goldman, chief of neurogenetics at the National Institute on Alcohol Abuse and Alcoholism. Although none has yet been shown to presage violence, "I believe the markers are there," he says. But he warns that "we're going to have to understand a whole lot more about the genetic, environmental and developmental origins of personality and psychiatric disease" before making use of the knowledge.

Yudofsky is less circumspect. "We are on the verge of a revolution in genetic medicine," he asserts. "The future will be to understand the genetics of aggressive disorders and to identify those who have greater tendencies to become violent."

Few researchers believe genetics alone will ever yield reliable predictors of behavior as complex and multifarious as harmful aggression. Still, the notion that biologists and sociologists might together be able to assemble a complicated model that can scientifically pick out those who pose the greatest threat of vicious attack seems to be gaining currency. Already some well-respected behavioral scientists are advocating a medical approach to crime control based on screening, diagnostic prediction and treatment. "A future generation will reconceptualize nontrivial recidivistic crime as a disorder," Raine predicted in his book, *The Psychopathology of Crime*.

Compulsory Treatment?

But the medical model of crime may be fraught with peril. When the "disease" is intolerable behavior that threatens society, will "treatment" necessarily be compulsory and indefinite? If, to reexamine Raine's hypothetical example, prediction models are judged reliable but "biological, social and cognitive intervention programs" are not,

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For Biological Studies, Minorities Need Not Apply

Scientists pursuing the role of biology in violent behavior have been twice shy since 1992, when shrill public criticism forced the National Institutes of Health to withdraw financial support of a conference on the ethical implications of "Genetic Factors in Crime" and compelled former health secretary Louis Sullivan to abort his proposed "Violence Initiative." Led by firebrand psychiatrist Peter Breggin, critics charged that in a society where blacks account for 12.4 percent of the population but 44.8 percent of arrests for violent crimes, such research plays into the hands of racists.

The controversy did little to dissuade scientists from their studies, which continue to grow in number. The NIH reinstated funding for the genetics conference and increased its budget for violence-related research to $58 million. Most Violence Initiative projects found support in other programs. In December 1994 the National Science Foundation began soliciting proposals for a $12-million, five-year violence research consortium.

But the political wrangling seems to have intimidated investigators from including minorities in any violence studies with a biological tinge—and from collecting medical data in multiracial studies. Designers of an 11,000-subject, eight-year study of the causes of crime in Chicago, for example, decided not to collect blood and urine samples when in 1994 Breggin organized rallies to block the project, says Felton Earls, a Harvard University professor and co-director of the study. As a result of such opposition and pressure, asserts Adrian Raine of the University of Southern California, "all the biological and genetic studies conducted to date have been done on whites. Scientifically, we can make no statements on the biological basis of violence and crime in blacks or Hispanics or Asians."

There is no reason to suspect that any genetic connection links race to antisocial behavior. But there is reason to be concerned that ostensibly objective biological studies, blindly ignoring social and cultural differences, could misguidedly reinforce racial stereotypes. Still, Earls, Raine and other researchers emphasize that biological factors, if they exist, are important only insofar as they protect individuals from—or make them vulnerable to—bad influences in their family, school and neighborhood. Research that excludes those who are most burdened by such pressures may be most expedient, but is it most useful? —*W. W. G.*

might eight-year-old boys be judged incorrigible before they have broken any law? Calls for screening are now heard more often. "There are areas where we can begin to incorporate biological approaches," Fishbein argues. "Delinquents need to be individually assessed." Masters claims that "we now know enough about the serotonergic system so that if we see a kid doing poorly in school, we ought to look at his serotonin levels."

In his article Jeffery emphasized that "attention must focus on the 5 percent of the delinquent population who commit 50 percent of the offenses.... This effort must identify high-risk persons at an early age and place them in treatment programs before they have committed the 10 to 20 major felonies characteristic of the career criminal."

Yudofsky suggests a concrete method to do this: "You could ask parents whether they consider their infant high-strung or hyperactive. Then screen more closely by challenging the infants with provocative situations." When kids respond too aggressively, he suggests "you could do careful neurologic testing and train the family how not to goad and fight them. Teach the children nonviolent ways to reduce frustration. And when these things don't work, consider medical interventions, such as beta blockers, anticonvulsants or lithium.

"We haven't done this research, but I have no doubt that it would make an enormous impact and would be immediately cost-effective," Yudofsky continues. While he bemoans a lack of drugs designed specifically to treat aggression, he sees a tremendous "opportunity for the pharmaceutical industry," which he maintains is "finally getting interested."

But some worry that voluntary screening for the good of the child might lead to mandatory screening for the protection of society. "It is one thing to convict someone of an offense and compel them to do something. It is another thing to go to someone who has not done anything wrong and say, 'You look like a high risk, so you have to do this,'" Akers observes. "There is a very clear ethical difference, but that is a very thin line that people, especially politicians, might cross over."

Even compelling convicted criminals to undergo treatment raises thorny ethical issues. Today the standards for proving that an offender is so mentally ill that he poses a danger to himself or others and thus can be incarcerated indefinitely are quite high. The medical model of violent crime threatens to lower those standards substantially. Indeed, Jeffery argues that "if we are to follow the medical model, we must use neurological examinations in place of the insanity defense and the concept of guilt. Criminals must be placed in medical clinics, not prisons." Fishbein says she is "beginning to think that treatment should be mandatory. We don't ask offenders whether they want to be incarcerated or executed. They should remain in a secure facility until they can show without a doubt that they are self-controlled." And if no effective treatments are available? "They should be held indefinitely," she says.

Moral Imperative

Unraveling the mystery of human behavior, just like untangling the human genetic code, creates a moral imperative to use that knowledge. To ignore it—to imprison without treatment those whom society defines as sick for the behavioral symptoms of their illness—is morally indefensible. But to replace a fixed term of punishment set by the conscience of a society with forced therapy based on the judgment of scientific experts is to invite even greater injustice. SA

Further Reading

THE PSYCHOPATHOLOGY OF CRIME. Adrian Raine. Academic Press, 1993.

UNDERSTANDING AND PREVENTING VIOLENCE. Edited by A. J. Reiss, Jr., and J. A. Roth. National Academy Press, 1993.

WHAT WORKS IN REDUCING ADOLESCENT VIOLENCE. Patrick Tolan and Nancy Guerra. Available from the Center for the Study and Prevention of Violence, University of Colorado, 1994.

Crime statistics and violence prevention program information are available on the World Wide Web at http://www.ojp.usdoj.gov/bjs

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